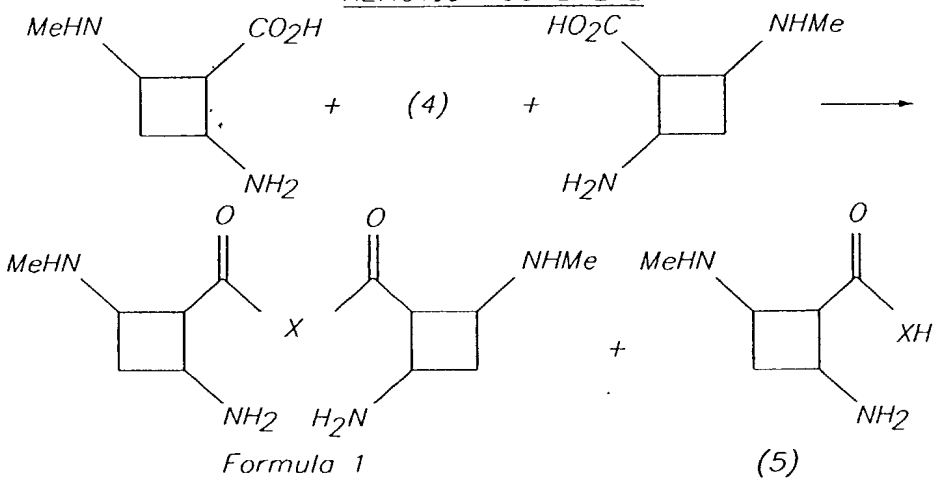
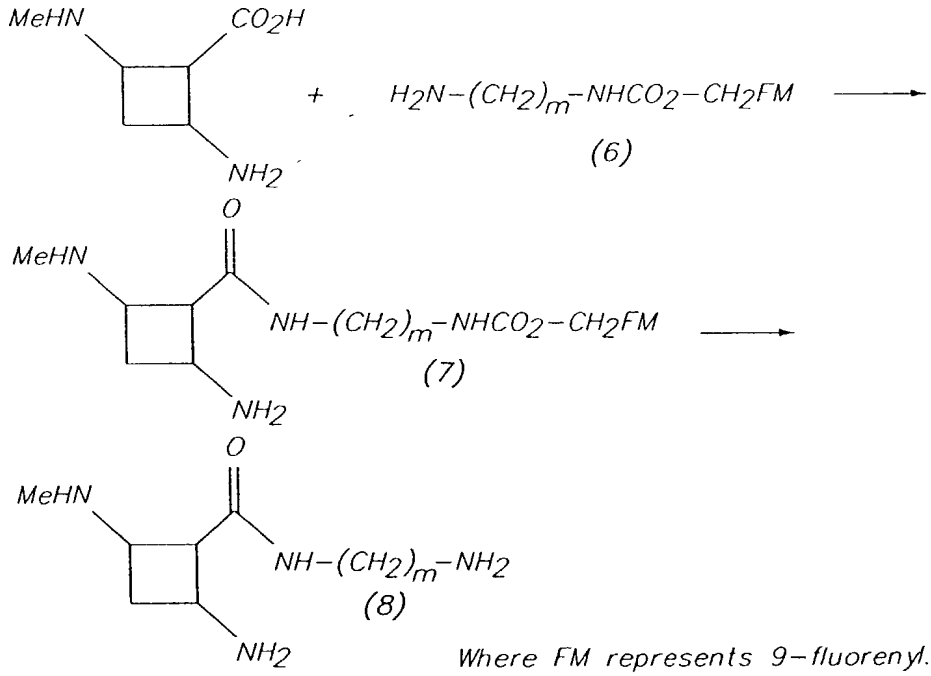
REACTION SCHEME 2



Formula 1 (5)

FIG. 1

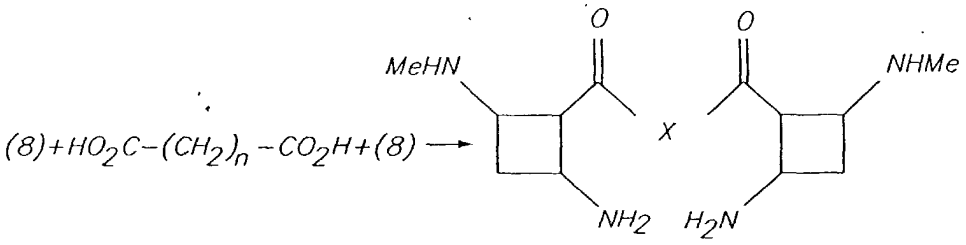
REACTION SCHEME 3



Where FM represents 9-fluorenyl., and m is an integer of 1-20

FIG. 2

REACTION SCHEME 4

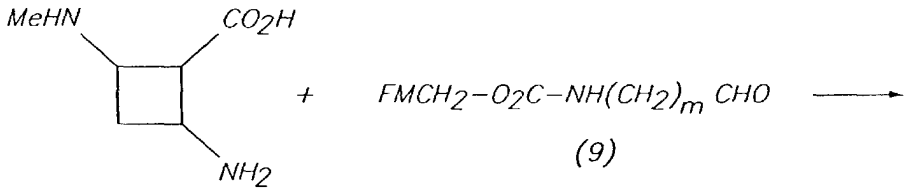


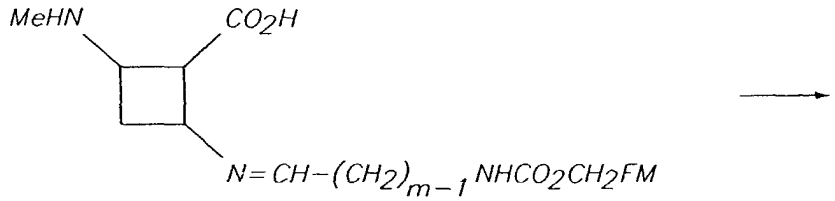
Formula 1

Where X is a linker of formula:
$-NH-(CH_2)_m\ NHC(O)(CH_2)_nC(O)NH(CH_2)_m\ -NH-$
in which m and n are independently integers of 1-20

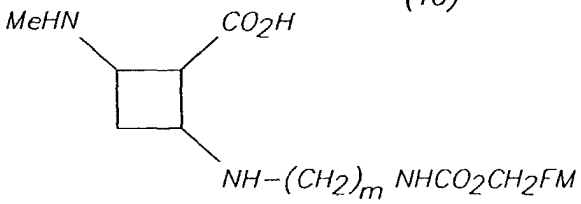
FIG. 3

REACTION SCHEME 5





(10)

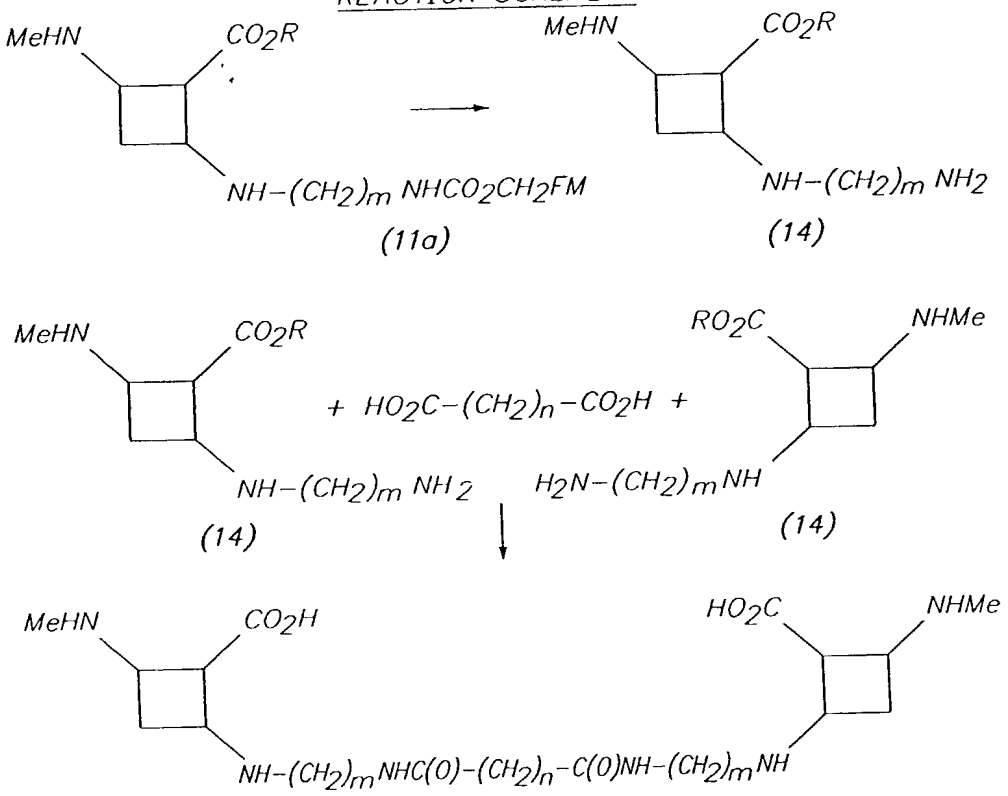


(11)

in which m is an integer of 1-20, and FM is 9-fluorenyl

FIG. 4

REACTION SCHEME 6



Formula 1

where R is a protecting group, such as an ester, m and n are as defined above, and FM is 9-fluorenyl

FIG. 5

REACTION SCHEME 7

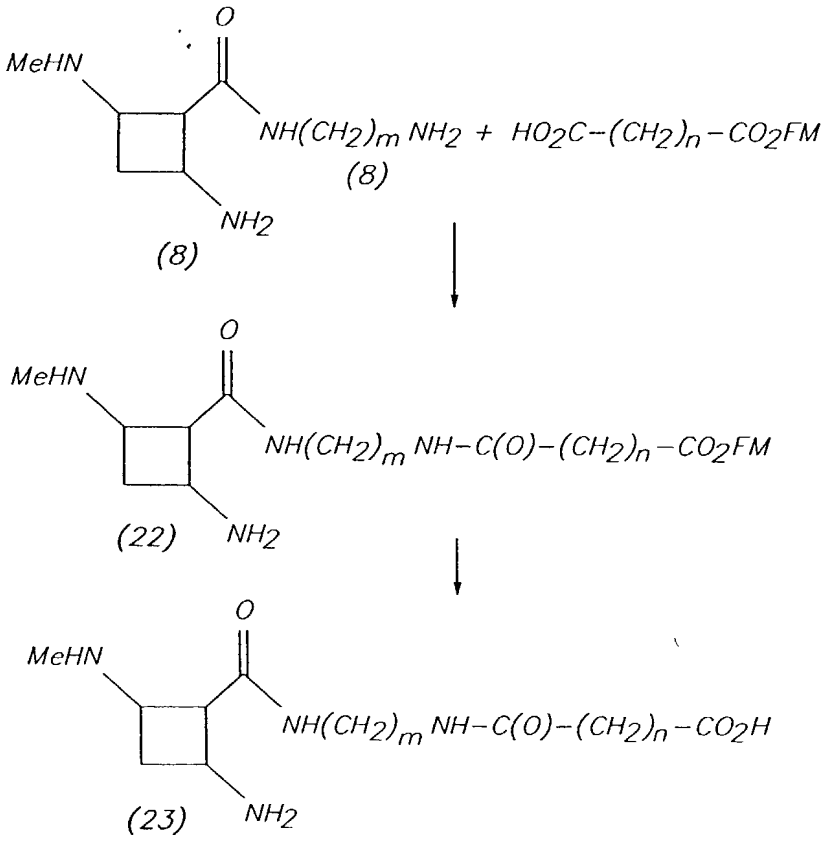
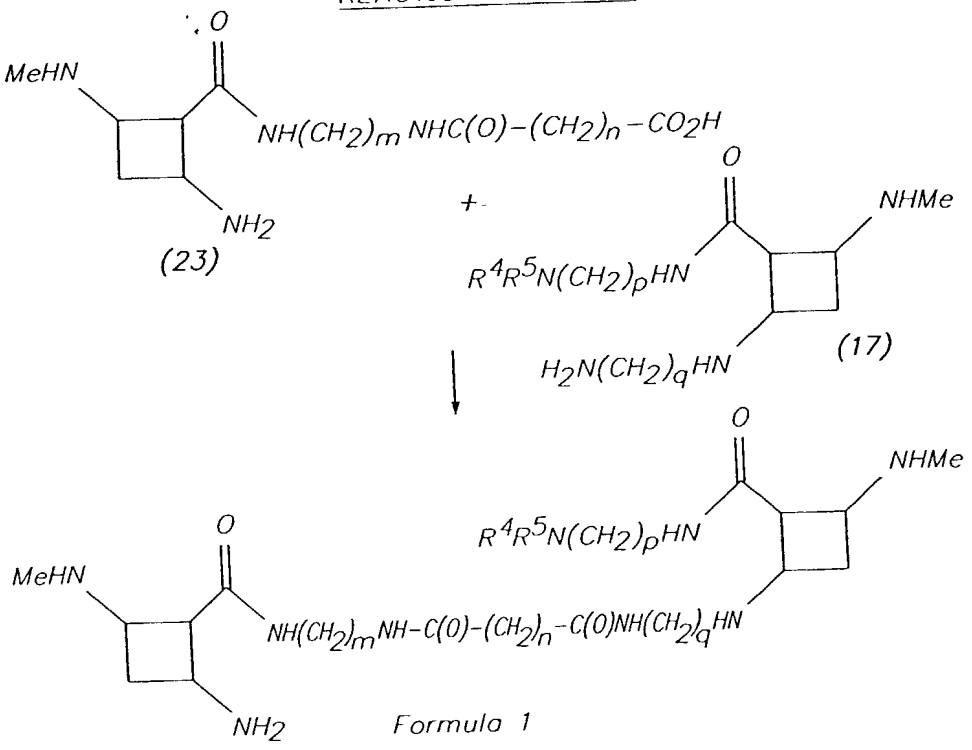


FIG. 6

REACTION SCHEME 8



Formula 1

FIG. 7

REACTION SCHEME 9

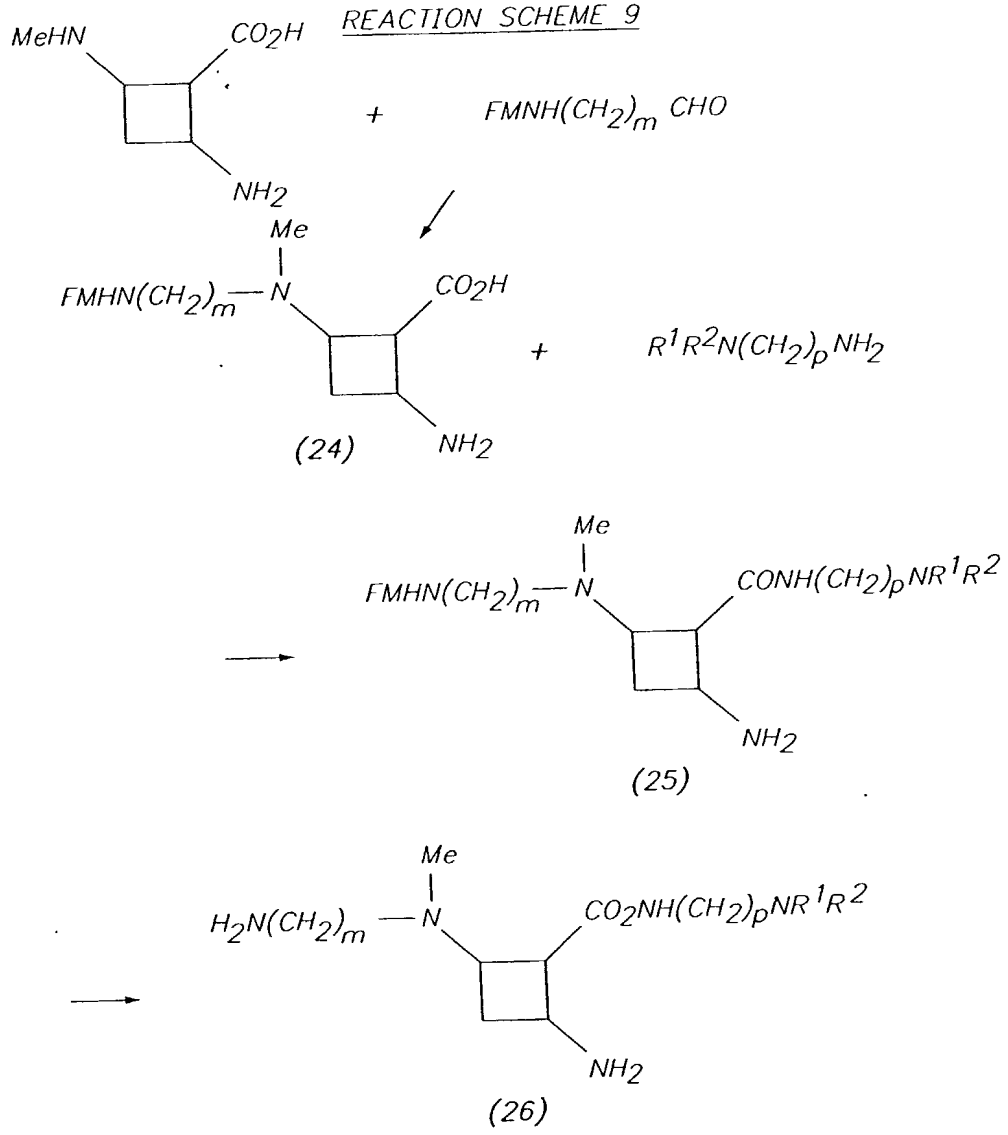


FIG. 8

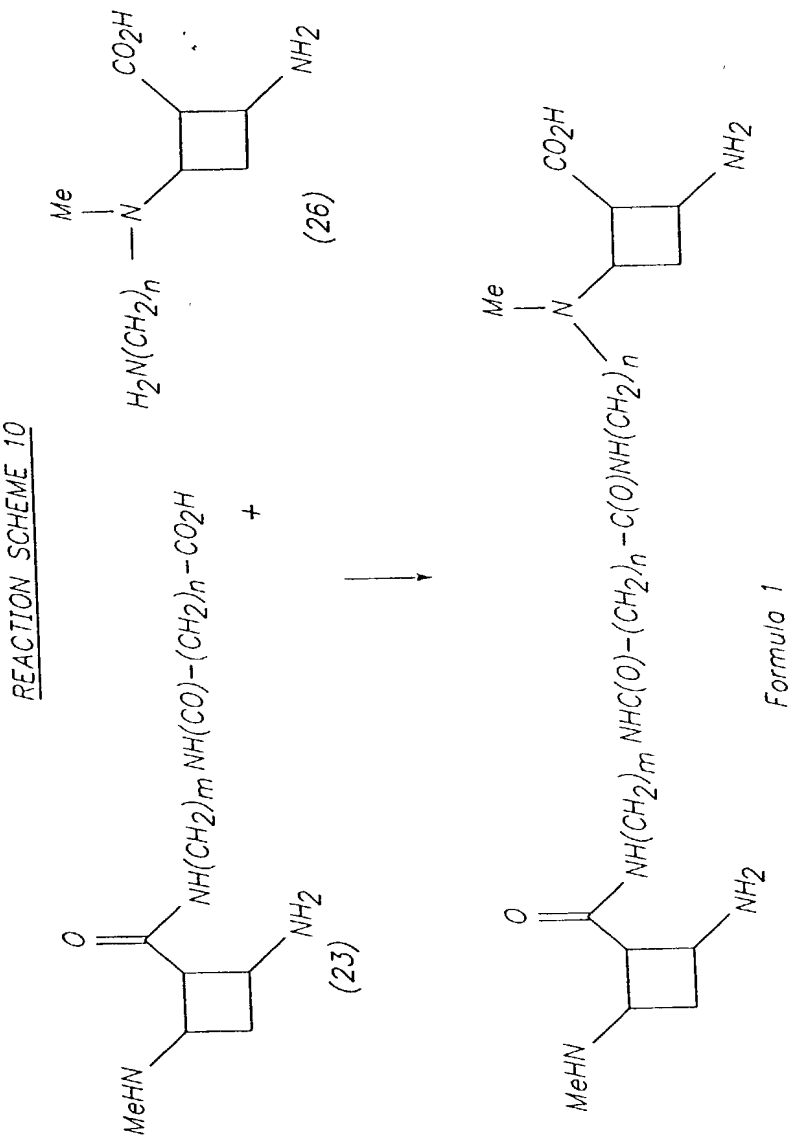
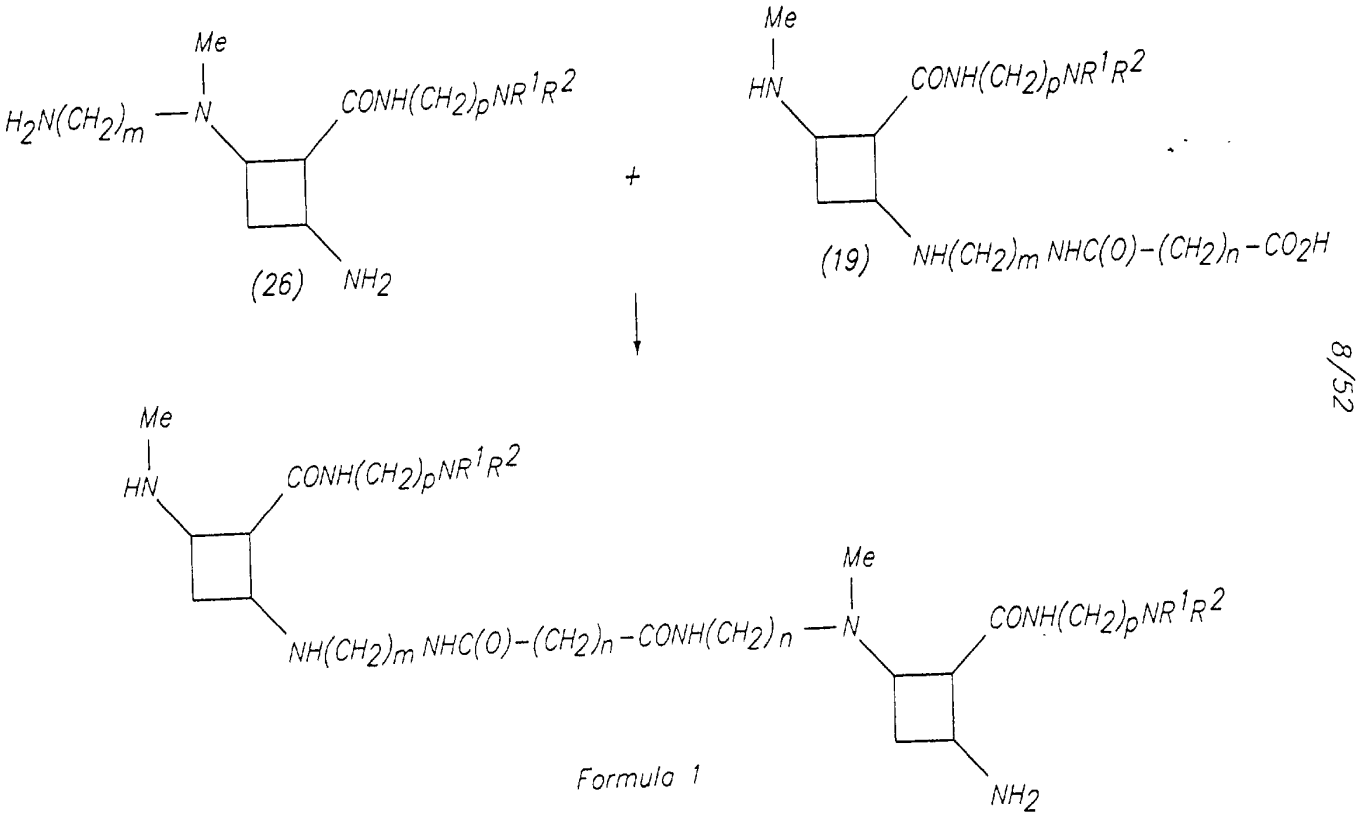

REACTION SCHEME 10
MeHN
O
NH(CH2)m NH(CO)-(CH2)n-CO2H
NH2
(23)
+
H2N(CH2)n
Me
N
CO2H
NH2
(26)
Formula 1

FIG. 9

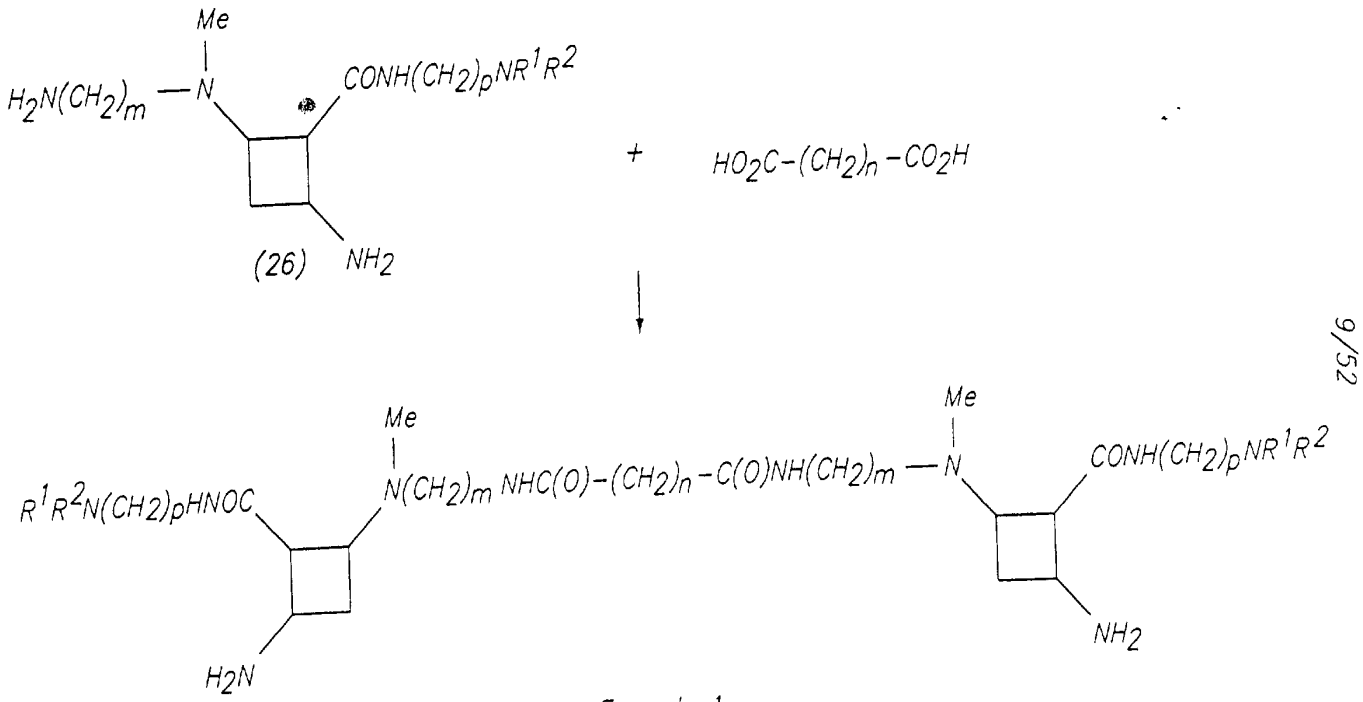
REACTION SCHEME 11



Formula 1

FIG. 10

REACTION SCHEME 12



Formula 1

FIG. 11

FIG. 12

Examples of dimeric display

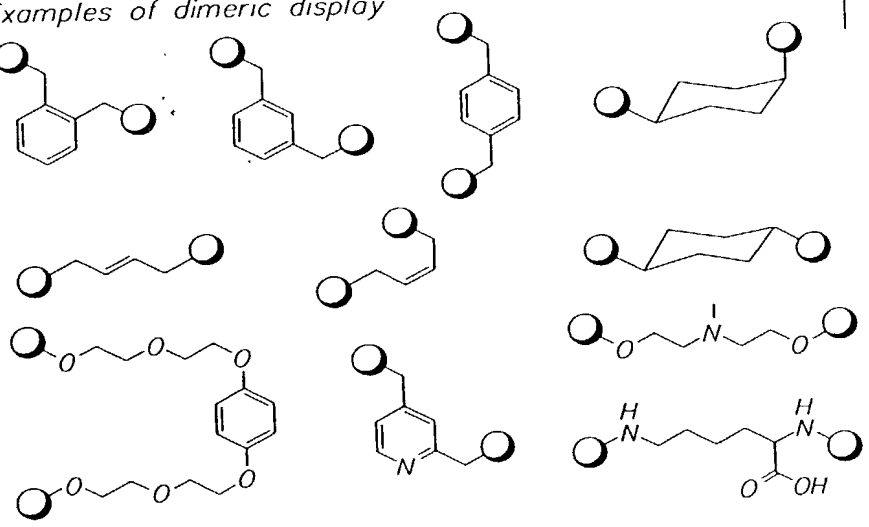


FIG. 13

Examples of trimeric display

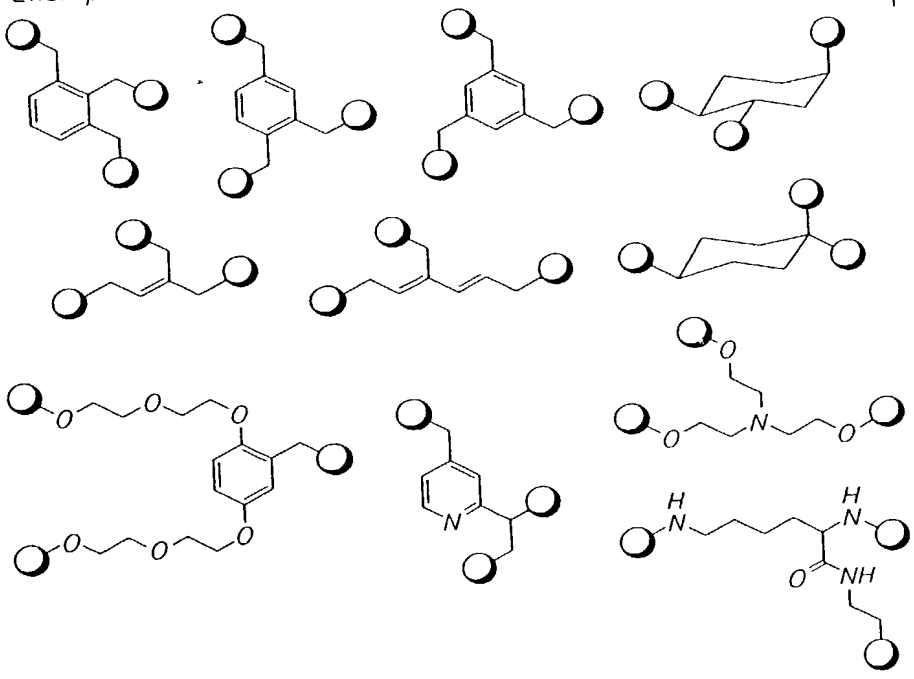


FIG. 14

Examples of tetrameric display

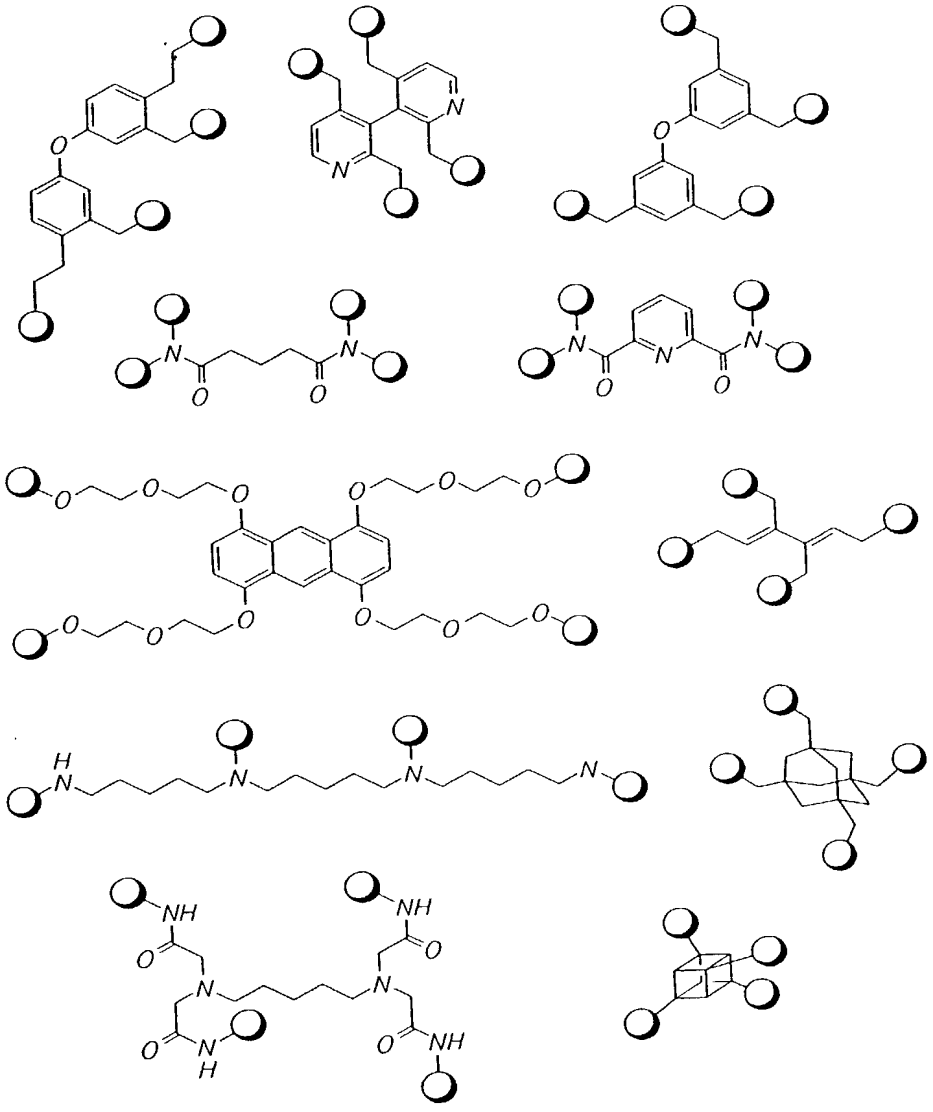


FIG. 15

Examples of higher order polyvalent display

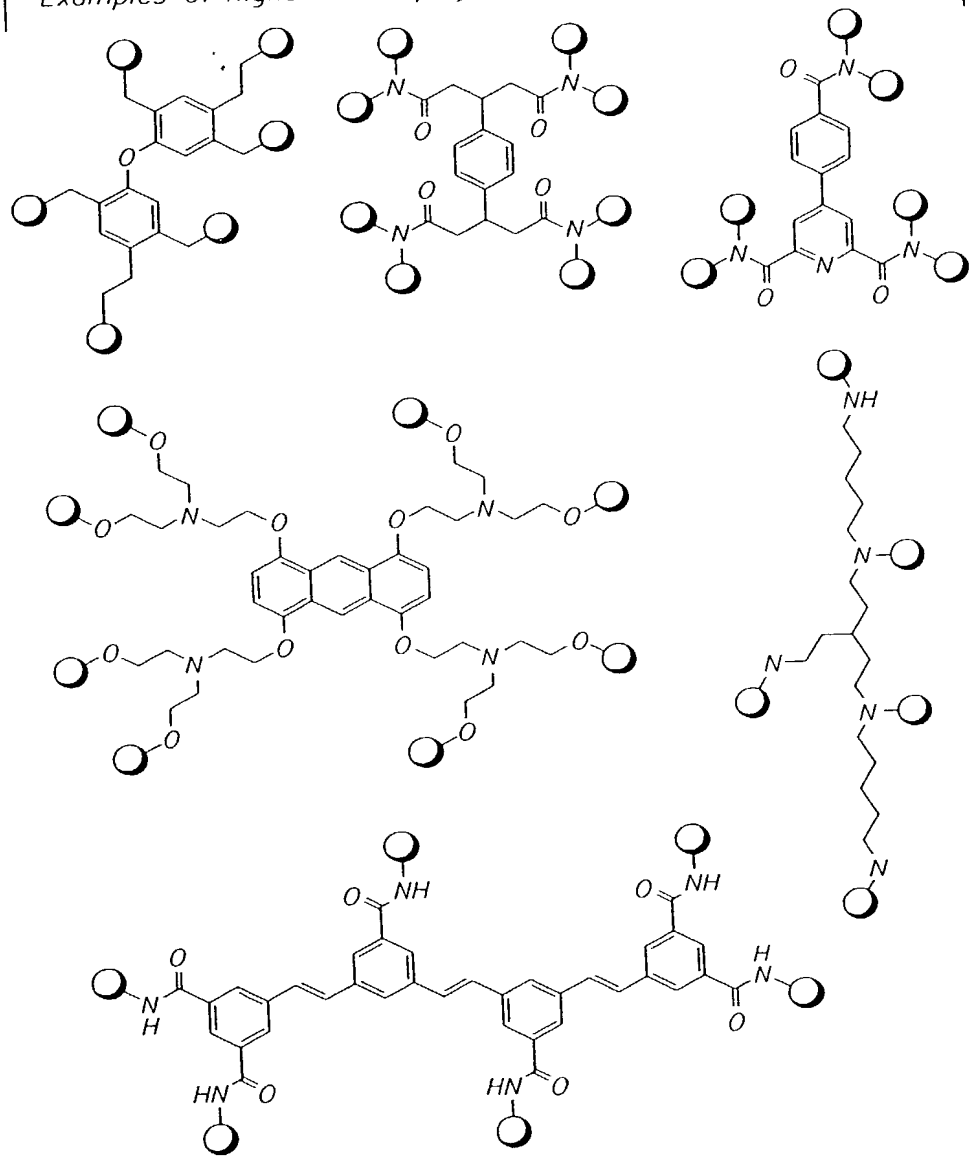
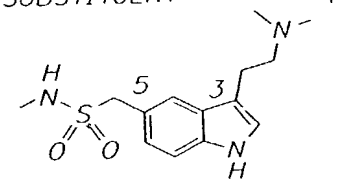
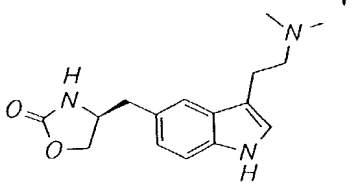


FIG. 16

C3 SUBSTITUENT

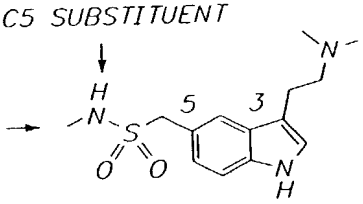


SUMATRIPTAN

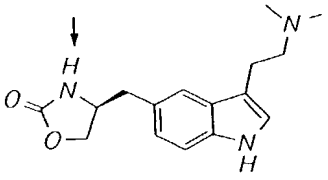


ZOLMITRIPTAN

C5 SUBSTITUENT



SUMATRIPTAN

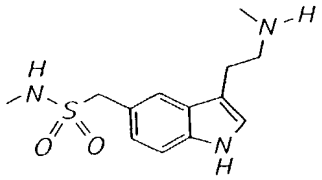


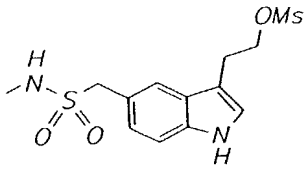
ZOLMITRIPTAN

FIG. 17

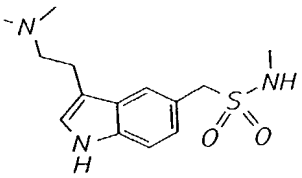
SUMATRIPTAN BUILDING BLOCKS

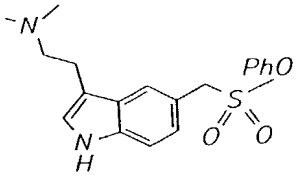
C3PharmacophoricBuilding Blocks



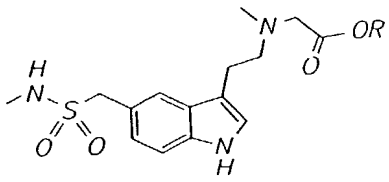


C5PharmacophoricBuilding Blocks





Pharmacophoric Building Blocks that contain a Spacer



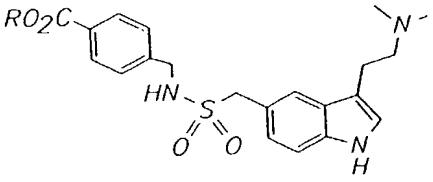
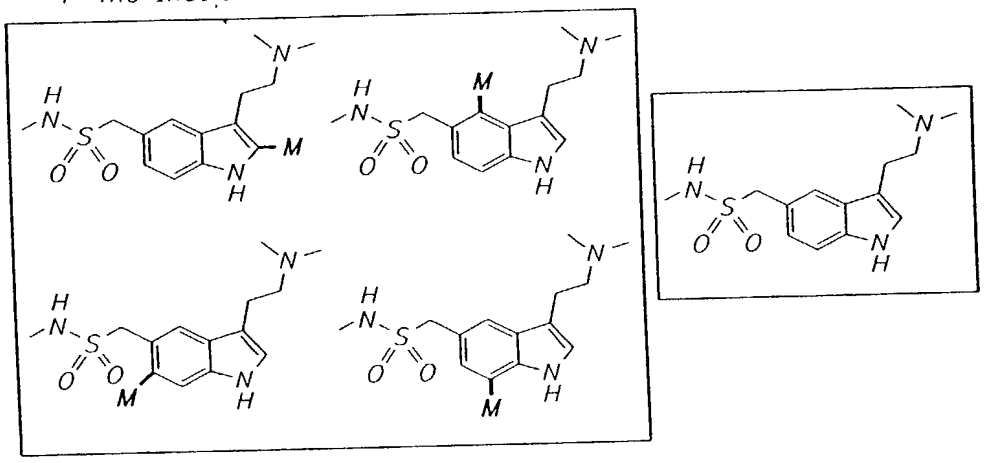


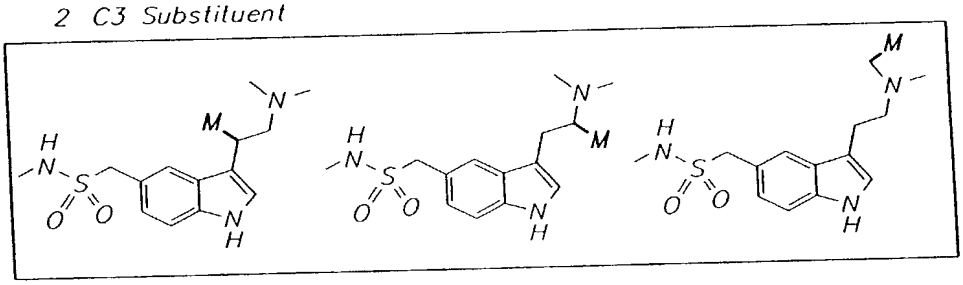
FIG. 18

MULTIVALOMERS OF SUMATRIPTAN

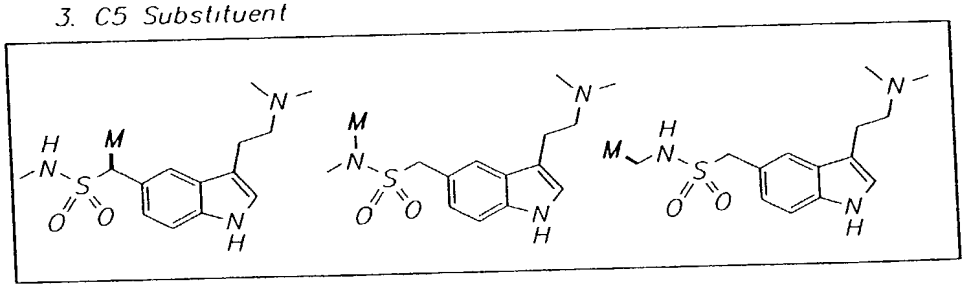
1 The Indole Core



2 C3 Substituent



3. C5 Substituent



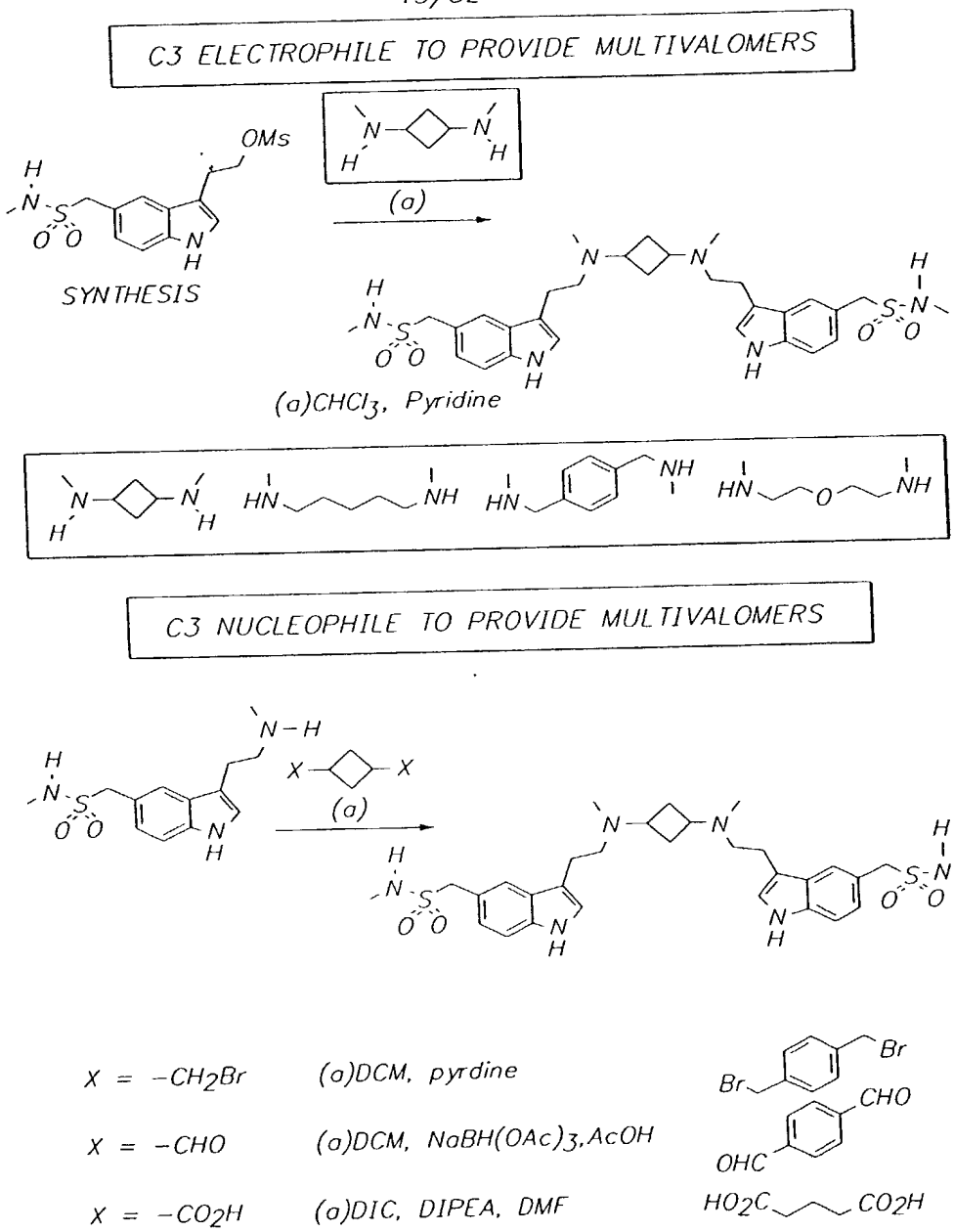
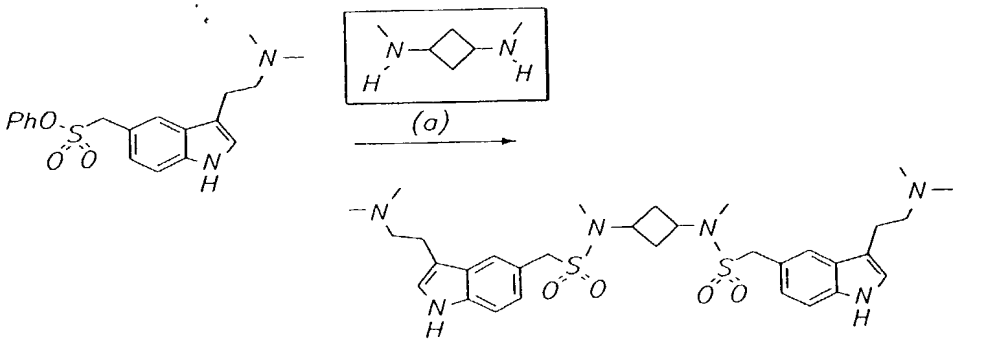

C3 ELECTROPHILE TO PROVIDE MULTIVALOMERS
OMs
SYNTHESIS
(a)
(a)CHCl3, Pyridine
C3 NUCLEOPHILE TO PROVIDE MULTIVALOMERS
X = -CH2Br
(a)DCM, pyrdine
X = -CHO
(a)DCM, NaBH(OAc)3,AcOH
X = -CO2H
(a)DIC, DIPEA, DMF
Br
CHO
OHC
HO2C
CO2H

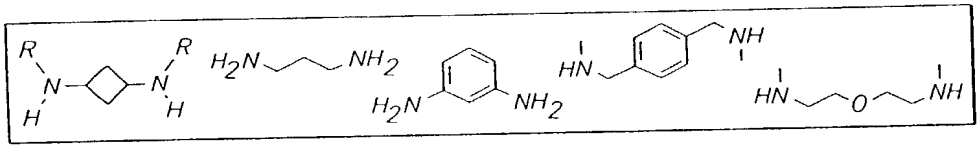
FIG. 19

C5 FUNCTIONALIZATION OF SUMATRIPTAN

Electrophilic Pharmacophoric Monovalomer



(a)DMF < DIPEA < RT



Nucleophilic Pharmacophoric Monovalomer

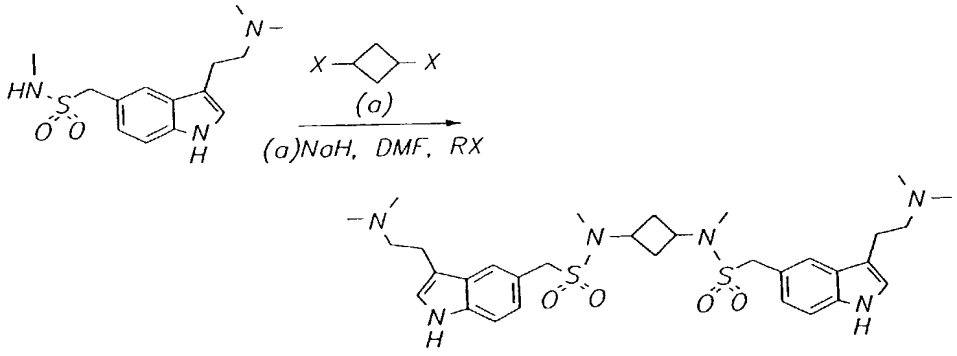


FIG. 20

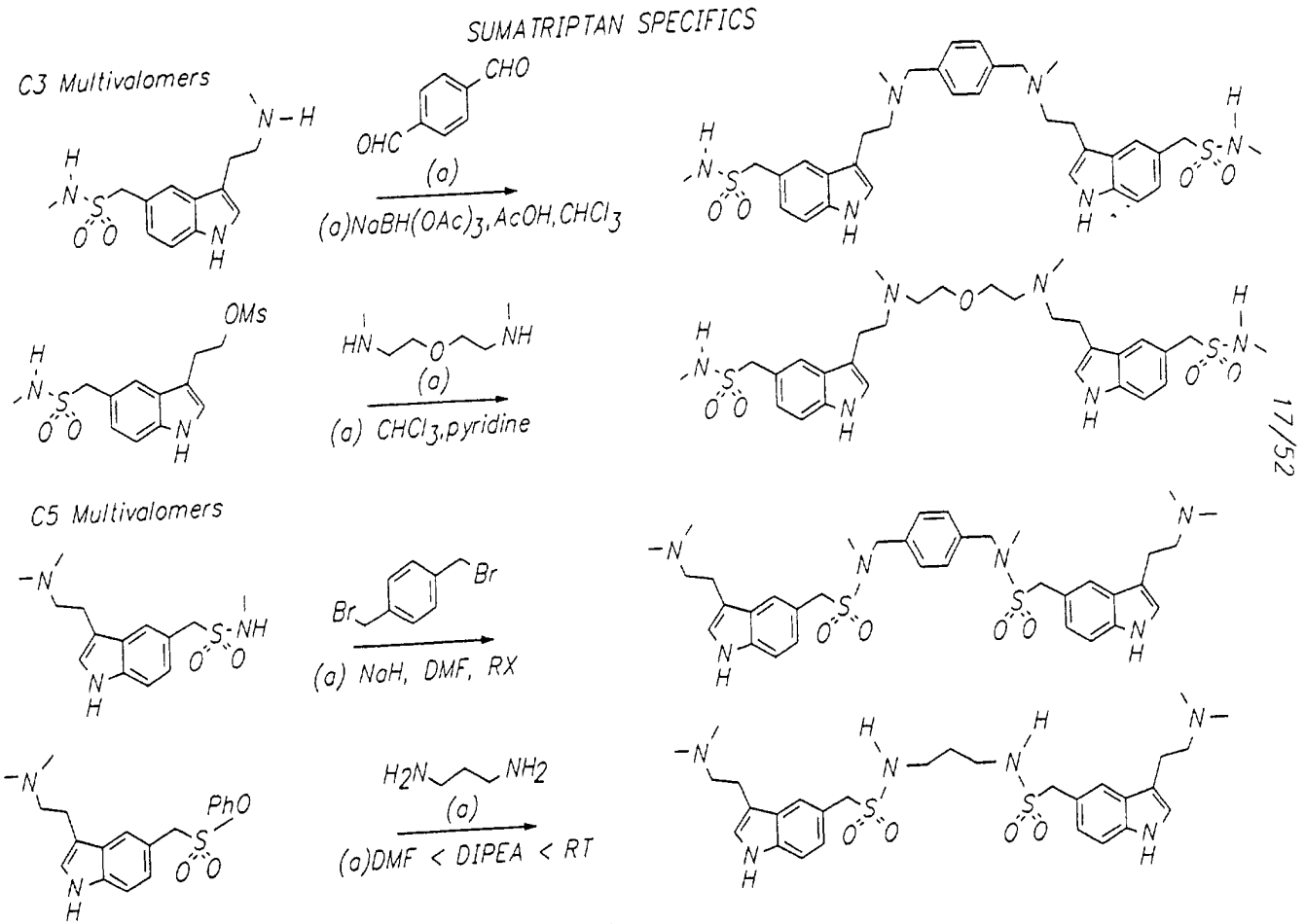

SUMATRIPTAN SPECIFICS
C3 Multivalomers
(a)NaBH(OAc)3, AcOH, CHCl3
(a) CHCl3, pyridine
C5 Multivalomers
(a) NaH, DMF, RX
(a)DMF < DIPEA < RT

FIG. 21

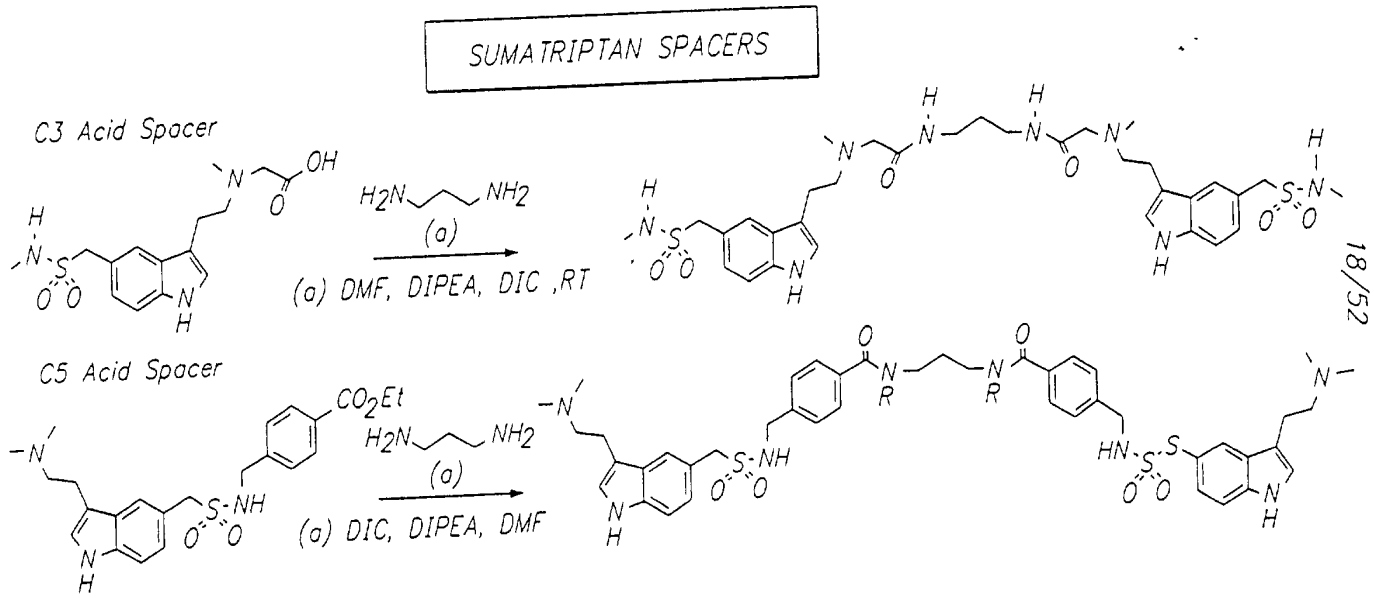
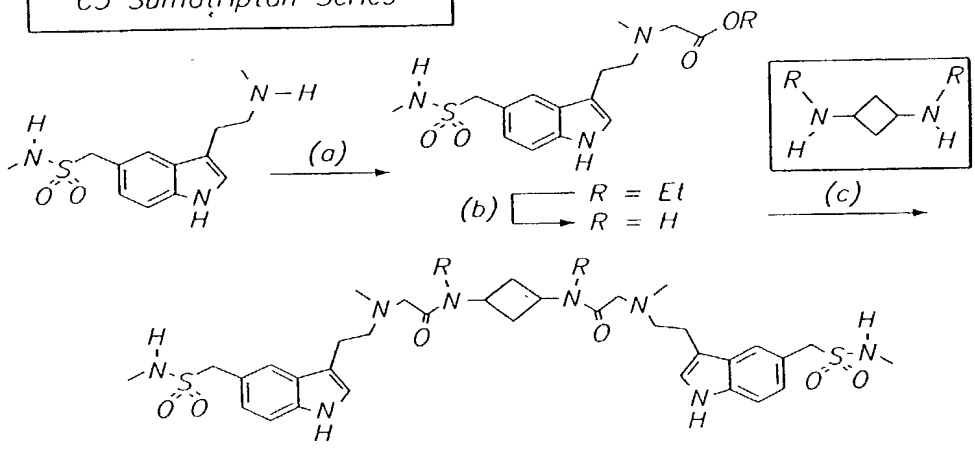

SUMATRIPTAN SPACERS
C3 Acid Spacer
OH
O
N
H
H2N
NH2
(a)
(a) DMF, DIPEA, DIC ,RT
C5 Acid Spacer
CO2Et
NH
(a) DIC, DIPEA, DMF
R

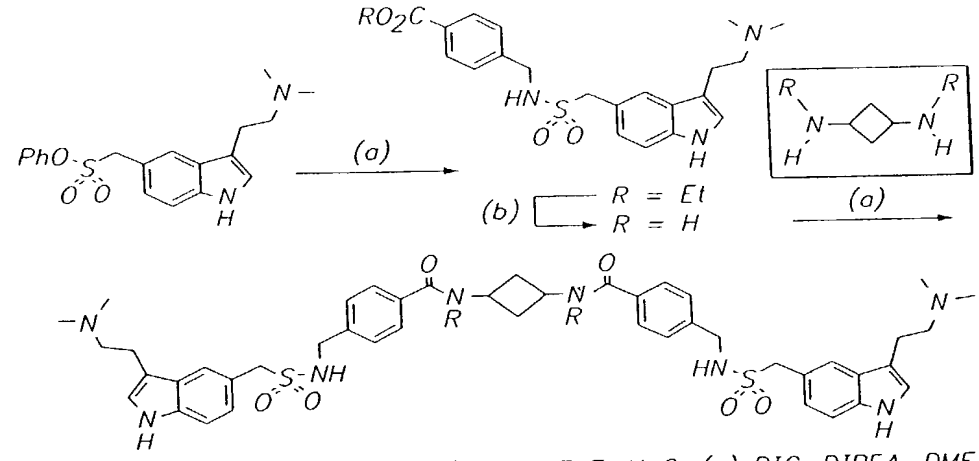
FIG. 22

Introduction of Spacer To Faciliate Multivalomer Formation

C3 Sumatriptan Series



C5 Sumatriptan Series



(a) DIPEA, DCM, $BrCH_2CO_2Et$ (b) LiOH, THF, H_2O, (c) DIC, DIPEA, DMF

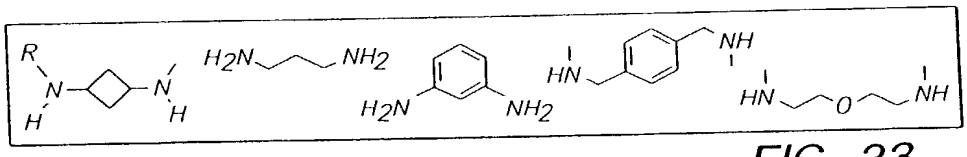
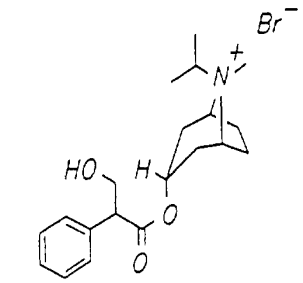
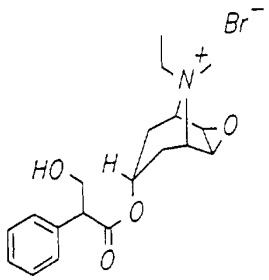


FIG. 23

MUSCARINIC ANTAGONISTS USED IN AIRWAY DISEASE

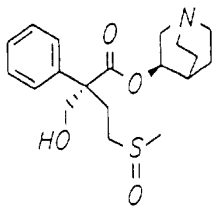


IPRATROPIUM BROMIDE

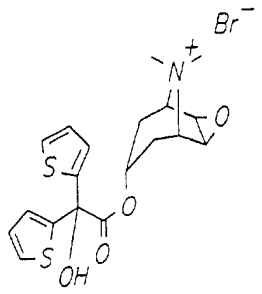


OXITROPIUM BROMIDE

I) Airway disease



REVATROPATE

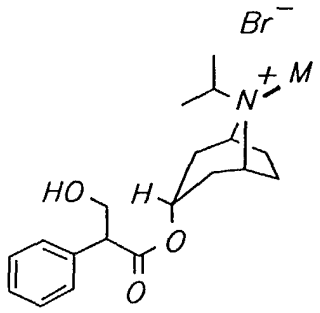


TIOTROPIUM BROMIDE

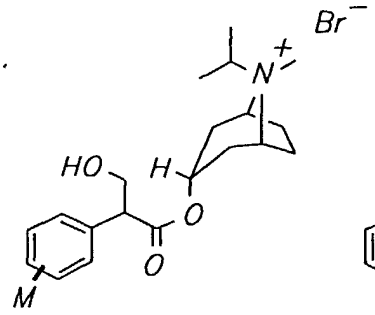
FIG. 24

SITES FOR DIMERIZATION

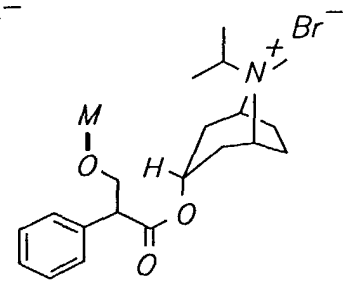
Nitrogen Atom of Tropane Core



Aromatic Ring

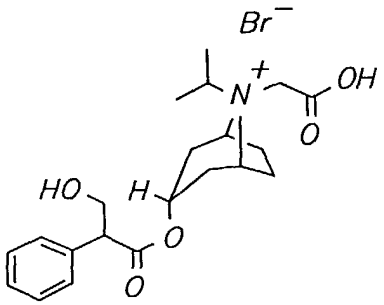


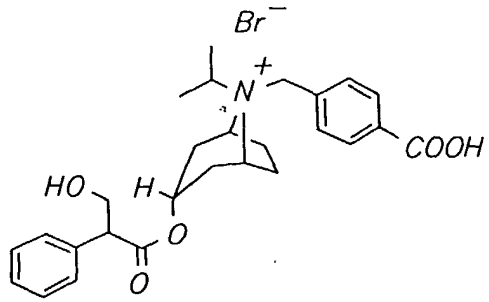
Primary Hydroxyl



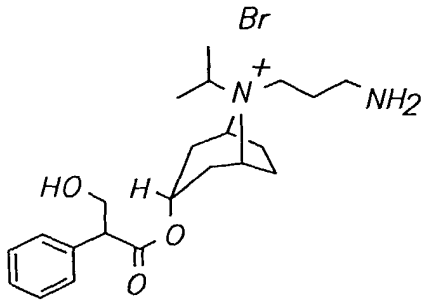
Suitable Pharmacophoric Building Blocks

Nitrogen Atom of Tropane Core
Acid Series





Amine Series



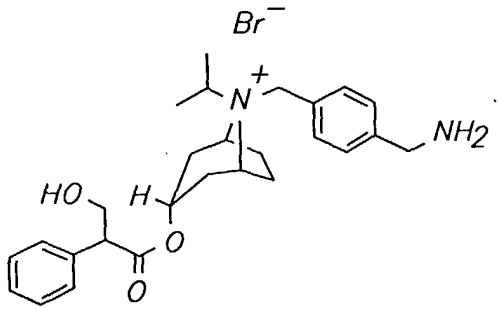
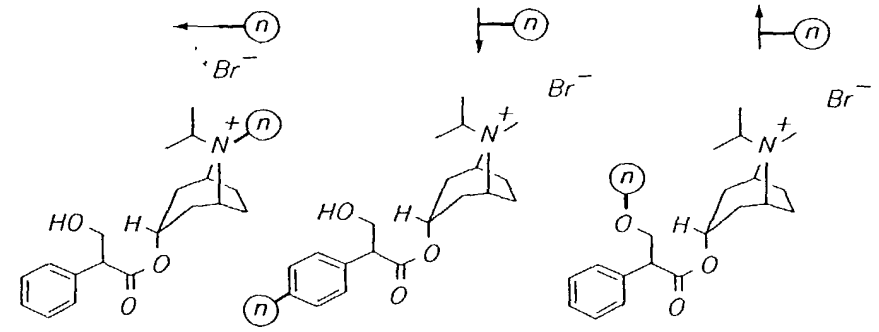


FIG. 25

Ipratropium Multivalomers 1– Different points of Attachment



n defines the valency of the multivalomer

◯ defines the framework core

⟶ distinguishes the differing points of attachment of ipratropium

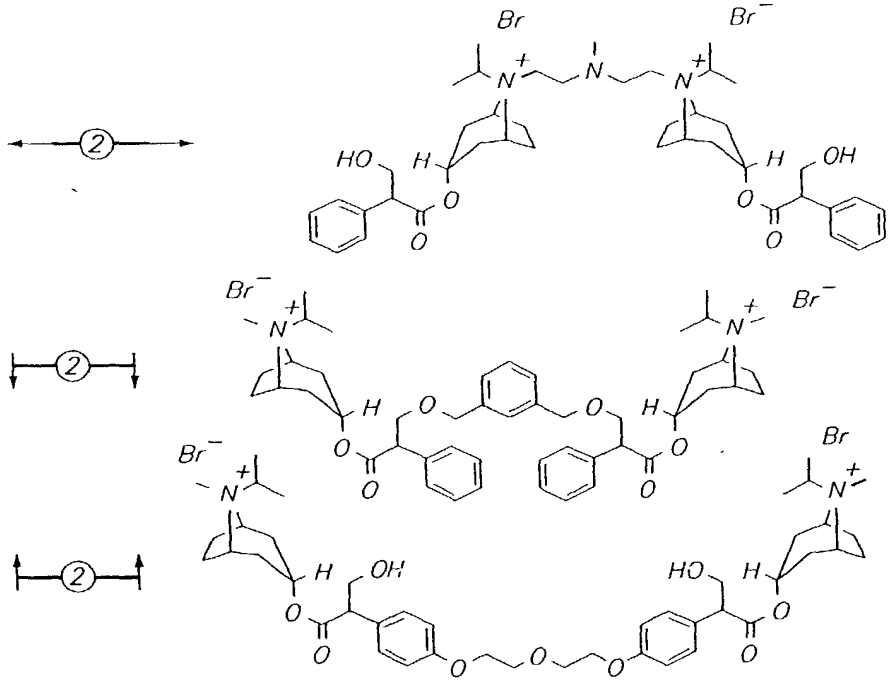


FIG. 26

Ipratropium Multivalomers 2-Alternative Framework Cores

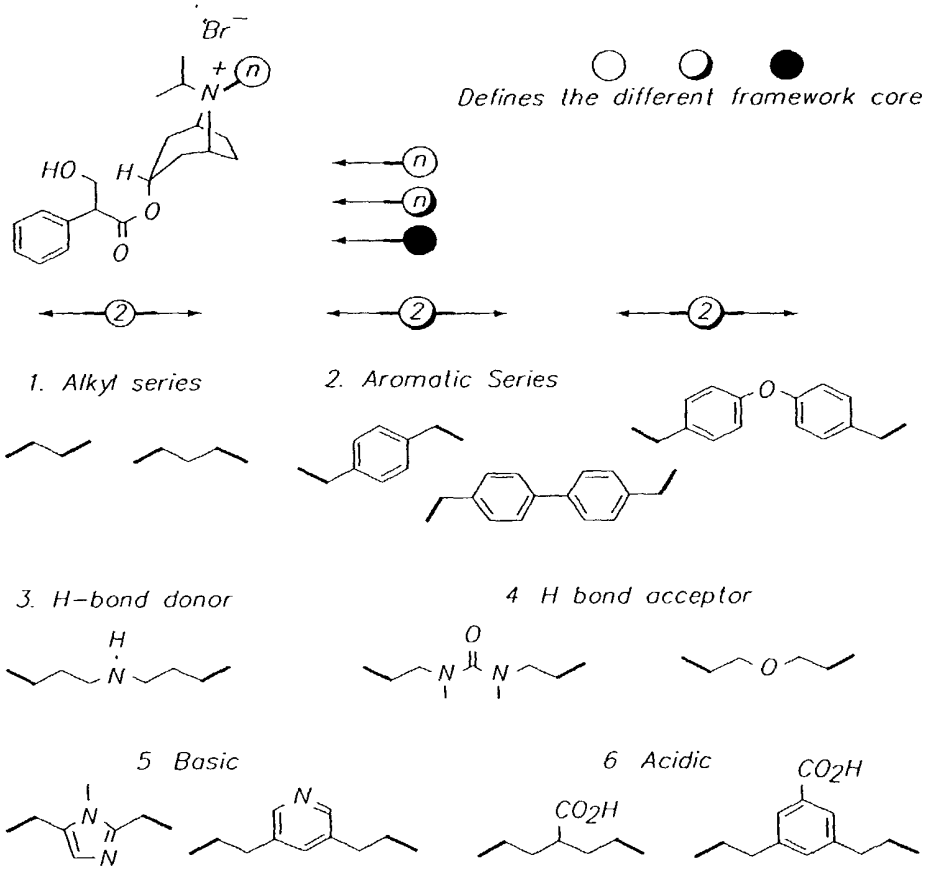


FIG. 27

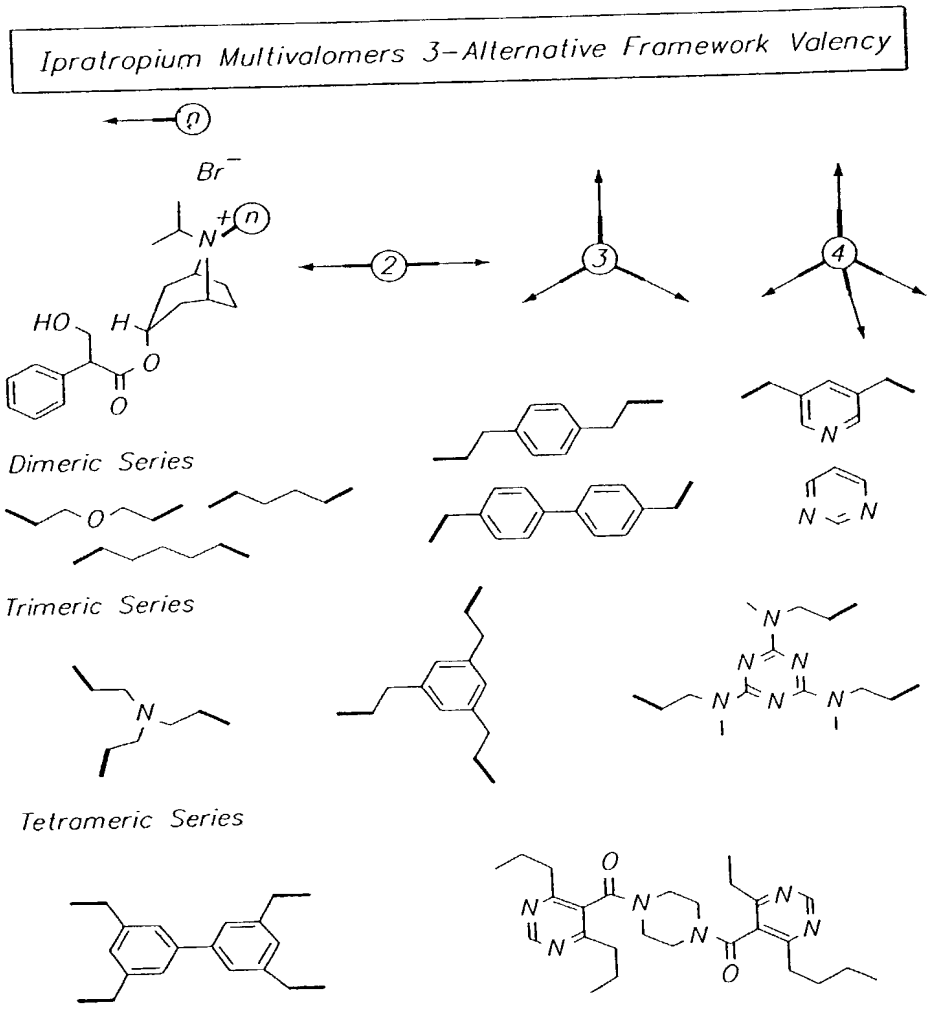

Ipratropium Multivalomers 3-Alternative Framework Valency
n
Br⁻
HO
H
O
O
2
3
4
Dimeric Series
Trimeric Series
Tetrameric Series

FIG. 28

Ipratropium Multivalomers 4–Relative Pharmacophore Orientation

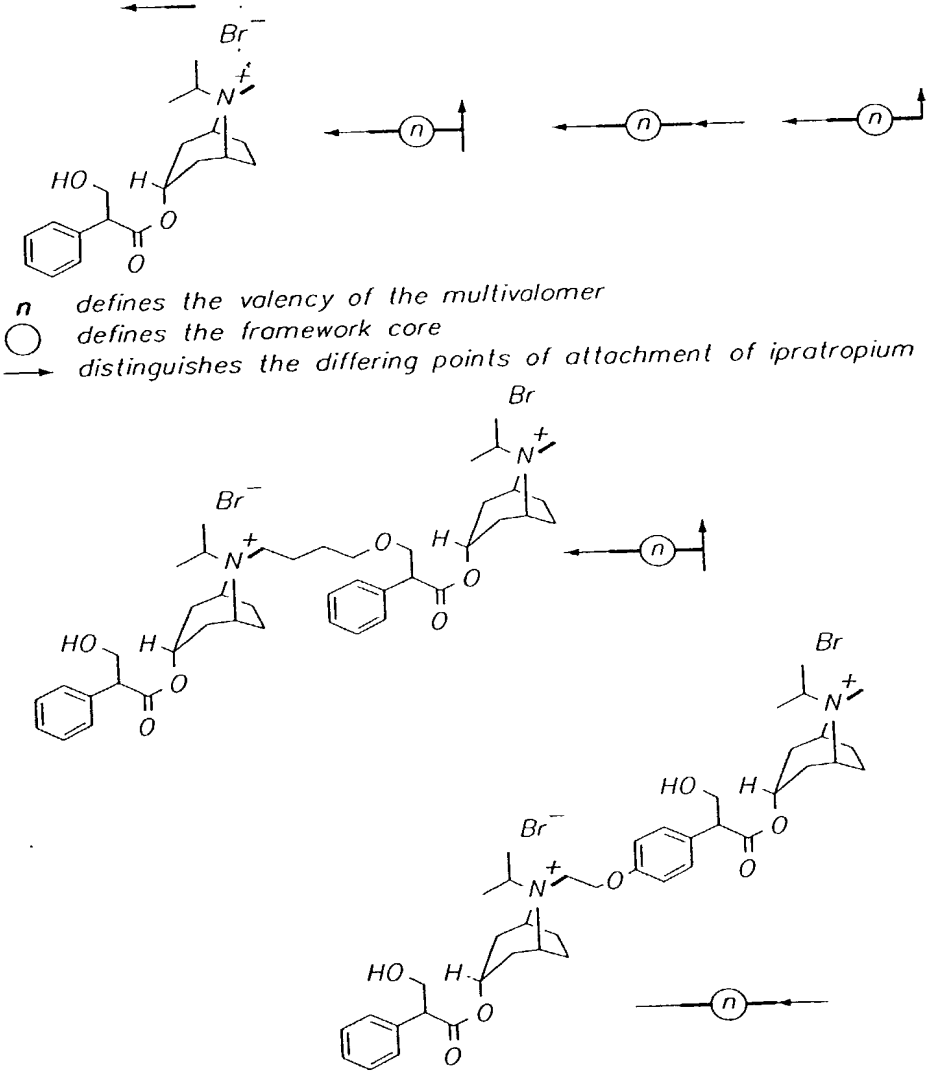


FIG. 29

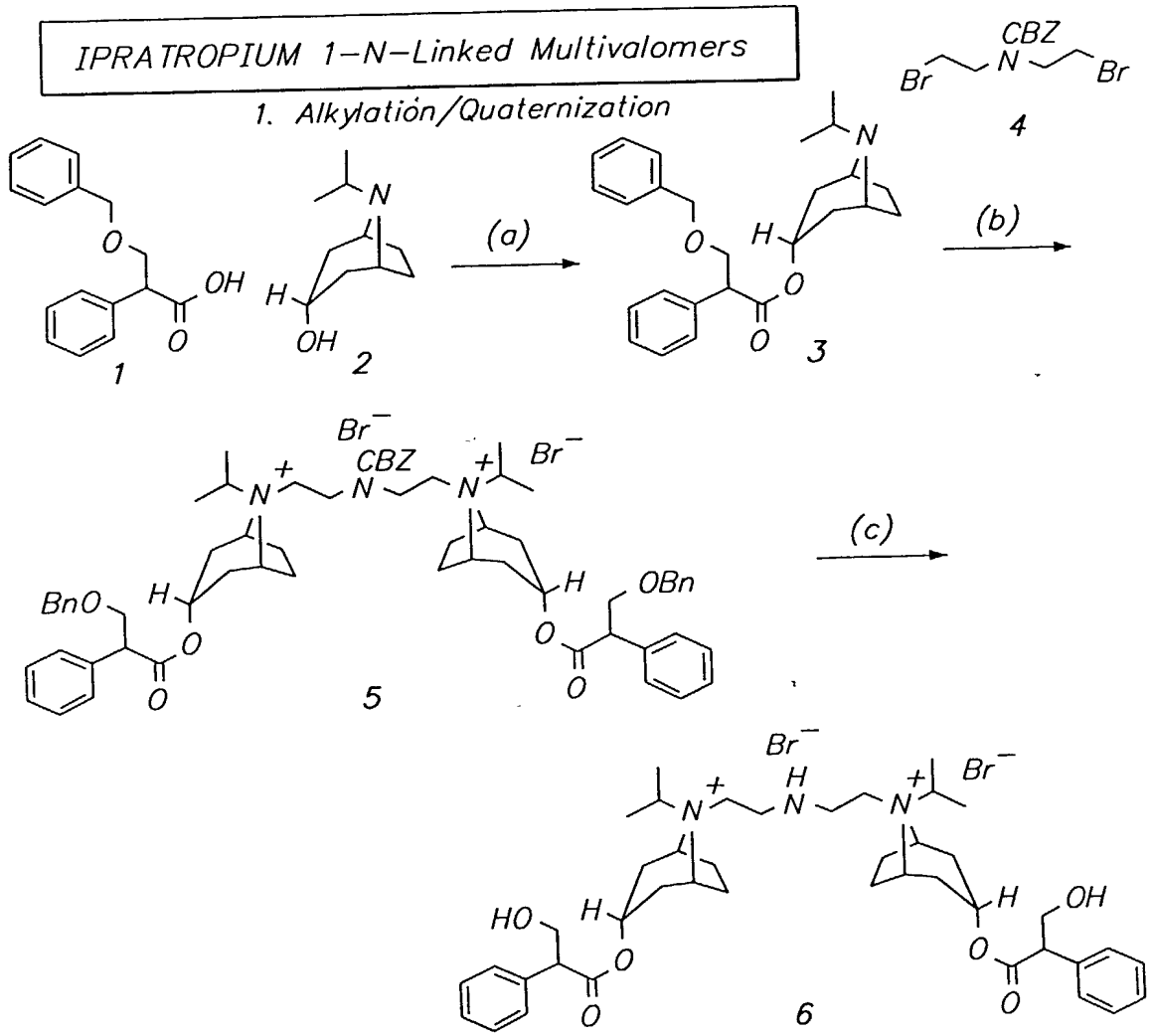
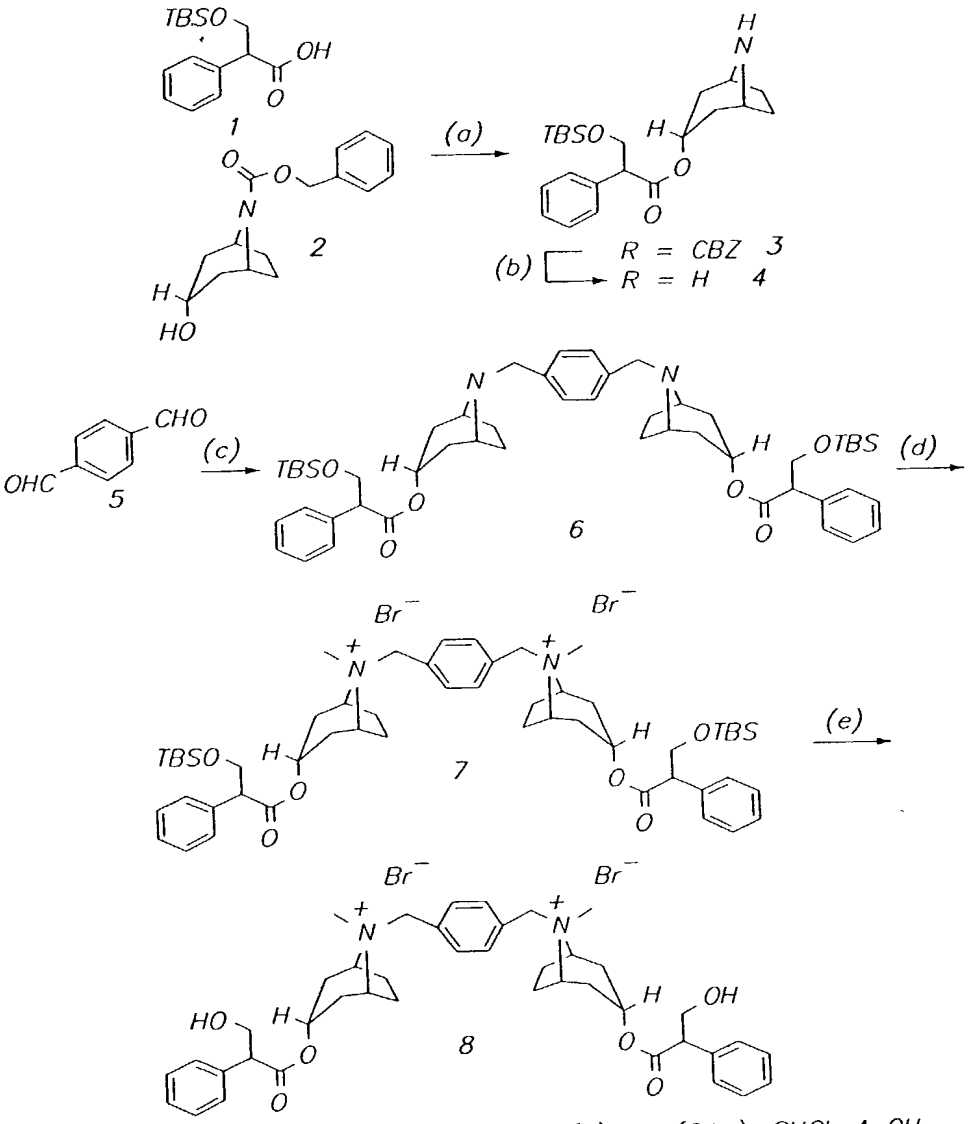

IPRATROPIUM 1–N–Linked Multivalomers
1. Alkylation/Quaternization
CBZ
Br
N
Br
4
(a)
(b)
(c)
1
2
3
5
6
Br⁻
CBZ
OBn
BnO
HO
OH
(a) DIC, DMAP, DMF (b) CHCl3 (c) Pd/C, H2,EtOAc

FIG. 30

IPRATROPIUM 2-N-Linked Multivalomers

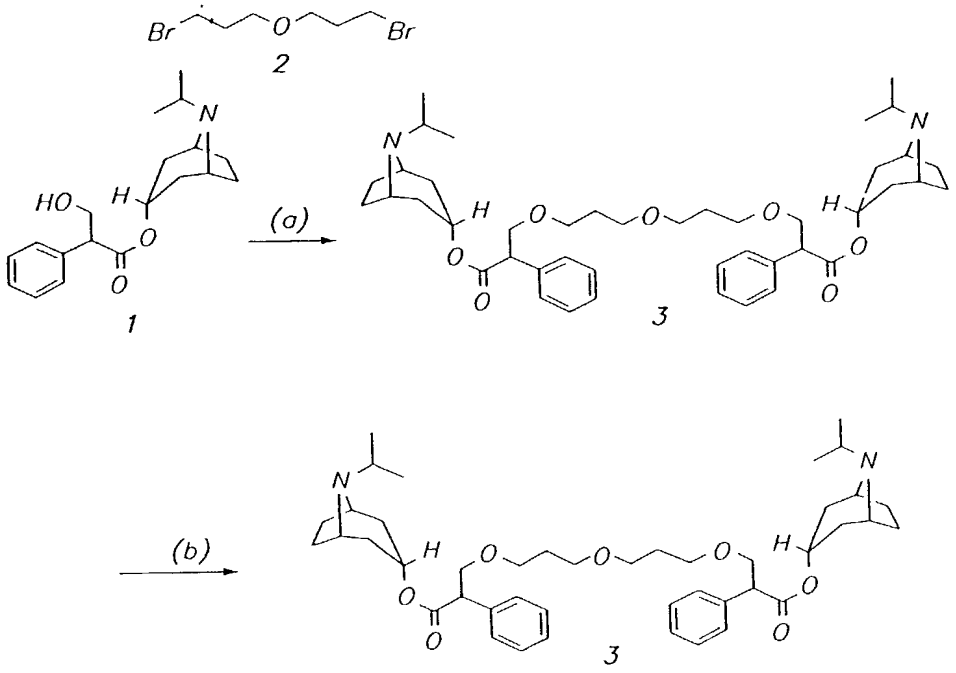
1. Reductive Amination/Quaternization



(a)DIC,DMF,DMF (b)Pd/C,H_2,EtOAC (c)$NaBH(OAc)_3$,$CHCl_3$,AcOH
(d)MeBr,$CHCl_3$(e)TBAF, THF

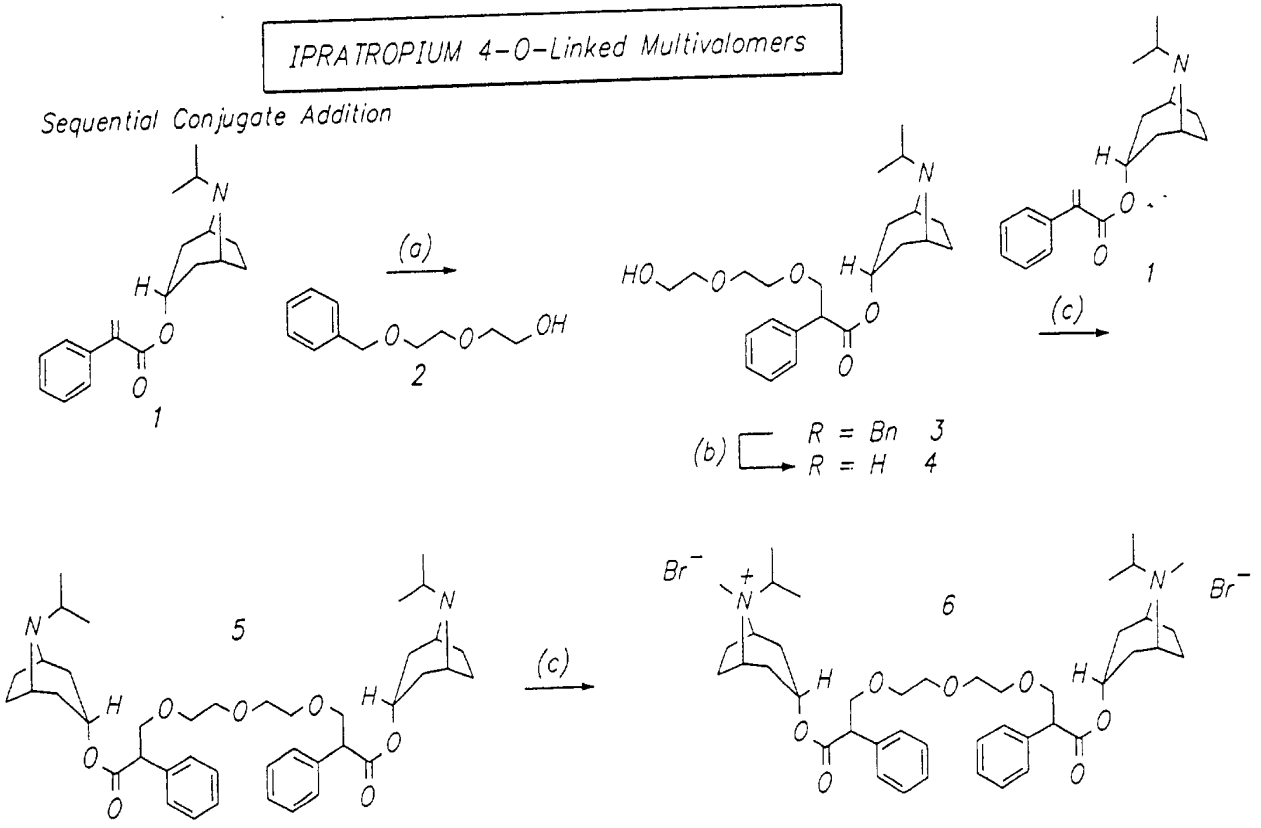
FIG. 31

IPRATROPIUM 3–O–Linked Multivalomers



(a)NaH, THF (b)MeBr, $CHCl_3$, REFLUX

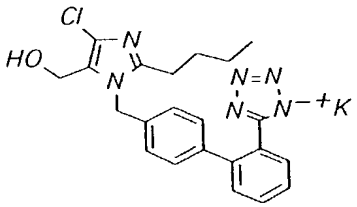
FIG. 32



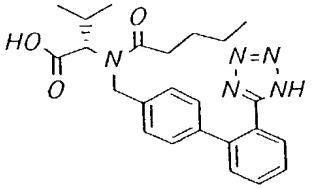
(a)NaH,DME,heat (b)Pd/C,H_2,EtOAc (c)NaH,DME,heat (d)MeBr,$CHCl_3$,heat

FIG. 33

AT1 RECEPTOR ANTAGONISTS

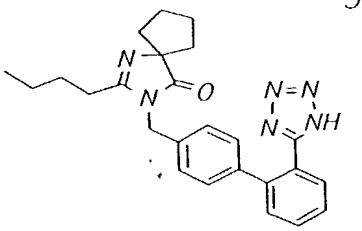


LOSARTAN (Cozaar)
(Dupont Merck)

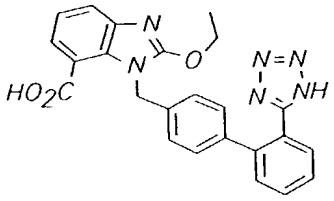


VALSARTAN (Diovan)
(Novartis)

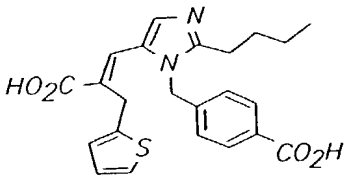
FIG. 34



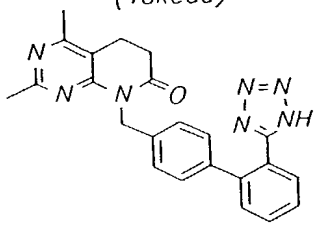
IRBESARTAN
(Sanofi)



CANDESARTAN (Atacand)
(Takeda)

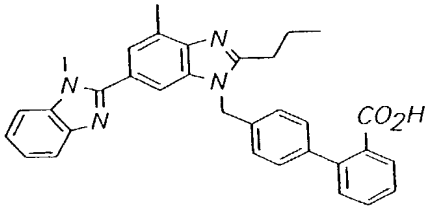


EPROSARTAN (Teveten)
(Smith KlineBeecham)

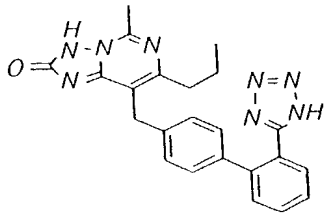


TASOSARTAN (Verdia)
(Wyerth-Ayerst)

FIG. 35



TELMISARTAN
(Boehringer Ingelhiem)
Phase III



RIPISARTAN
(Bristol Myers Squibb)
Phase II

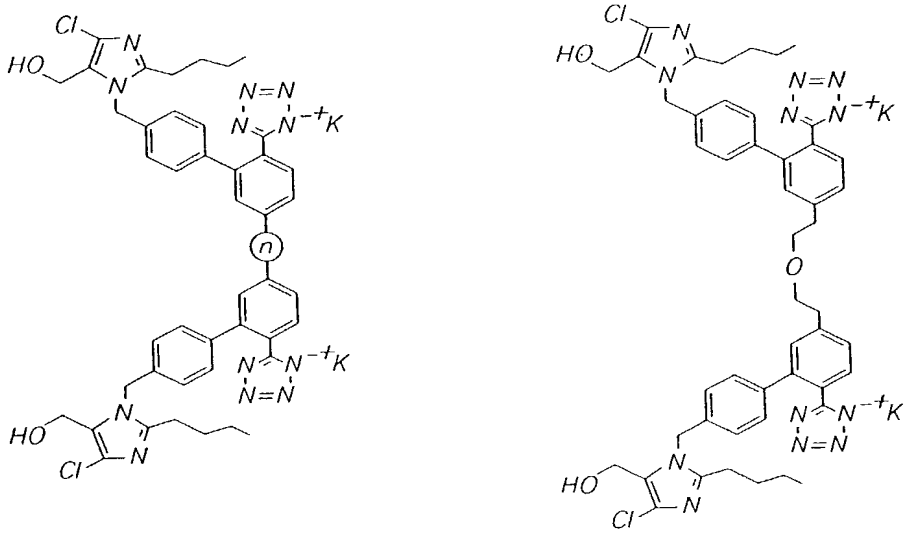
Phase II
CS-866 Sankyo
DA-727 Daiichi
KRH-594 Wakunga
LR-B/081 Lusofarmaco
TAK-536 Takeda
YM-358 Yamanouchi

FIG. 36

FIG. 37

Losartan Multivalomers 1–Differing Points of Attachment

1. Aryl Linked Multivalomers



2. Butyl Linked Multivalomers

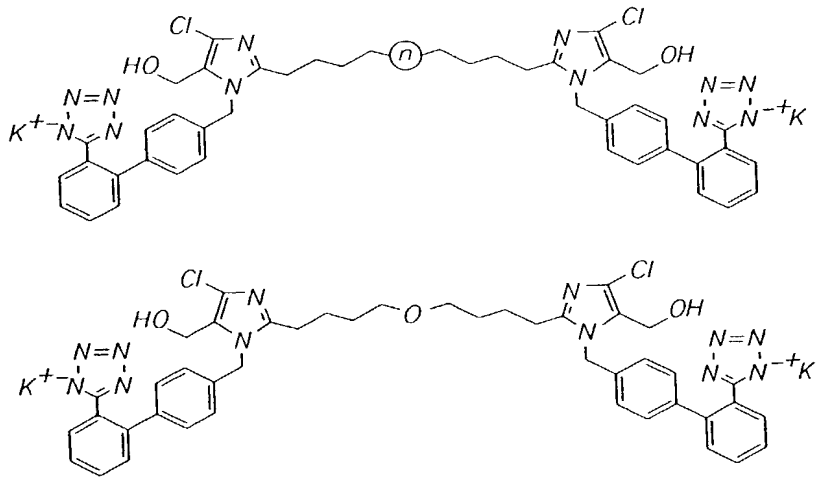
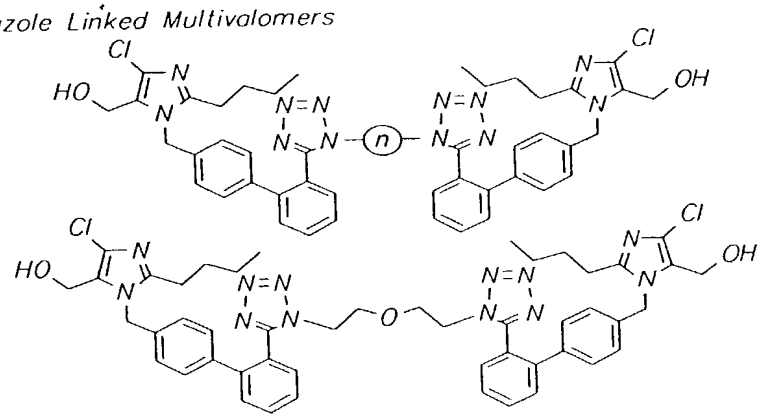


FIG. 38

Losartan Multivalomers 1–Differing Points of Attachment

1. Tetrazole Linked Multivalomers



2. Aryl Linked Multivalomers

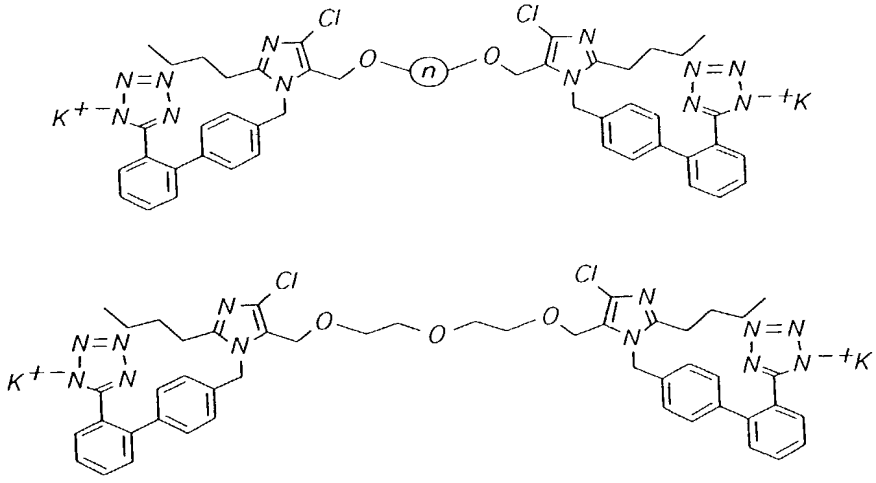


FIG. 39

Lorsartan Multivalomers 2-Differing Valency of Multivalomer

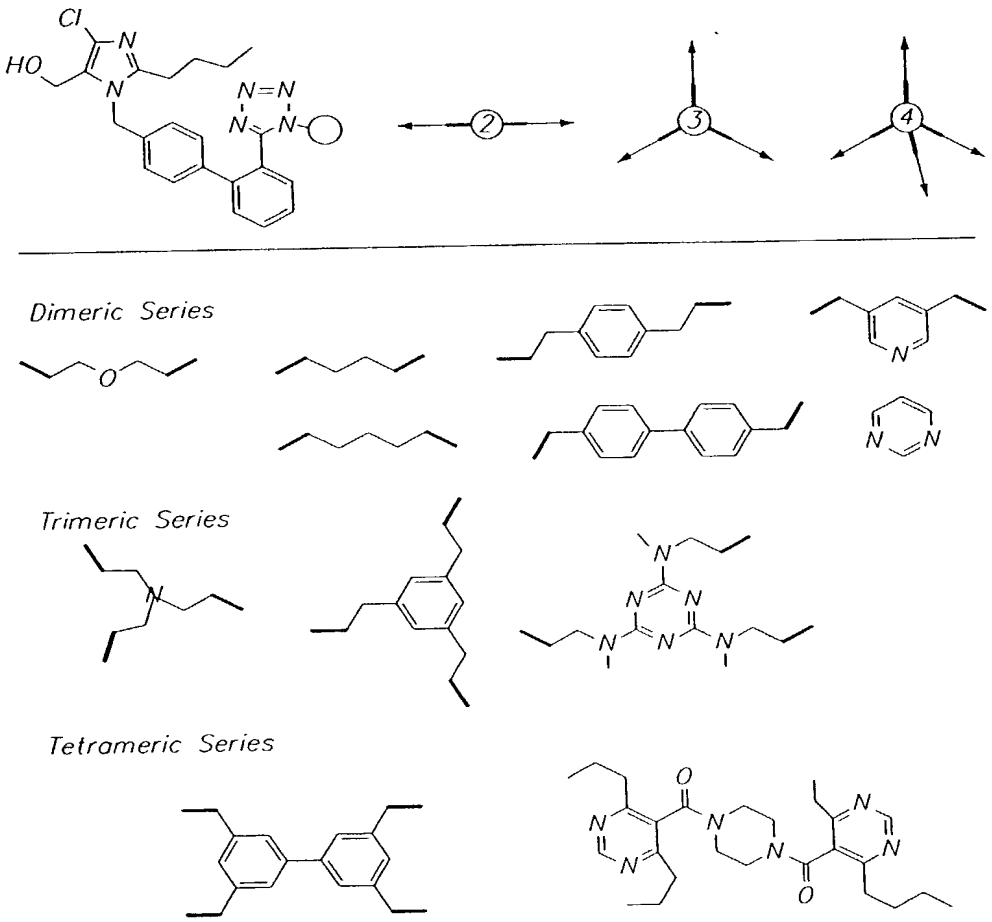


FIG. 40

Lorsartan Multivalomers 3-Differing Framework Building Blocks

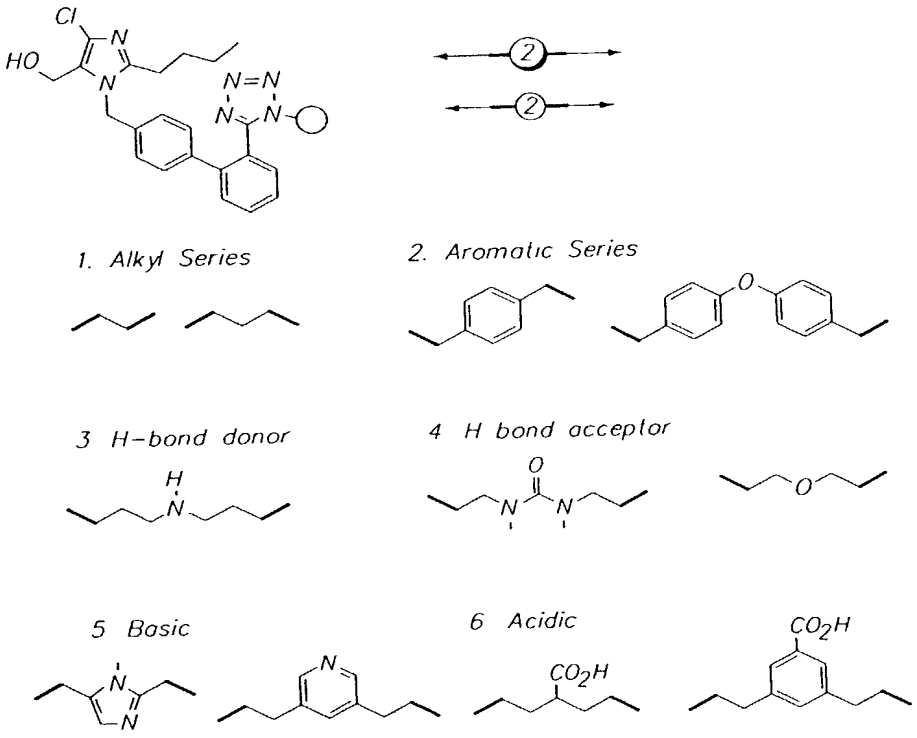


FIG. 41

Losartan Multivalomers 4-Different Relative Connectivity

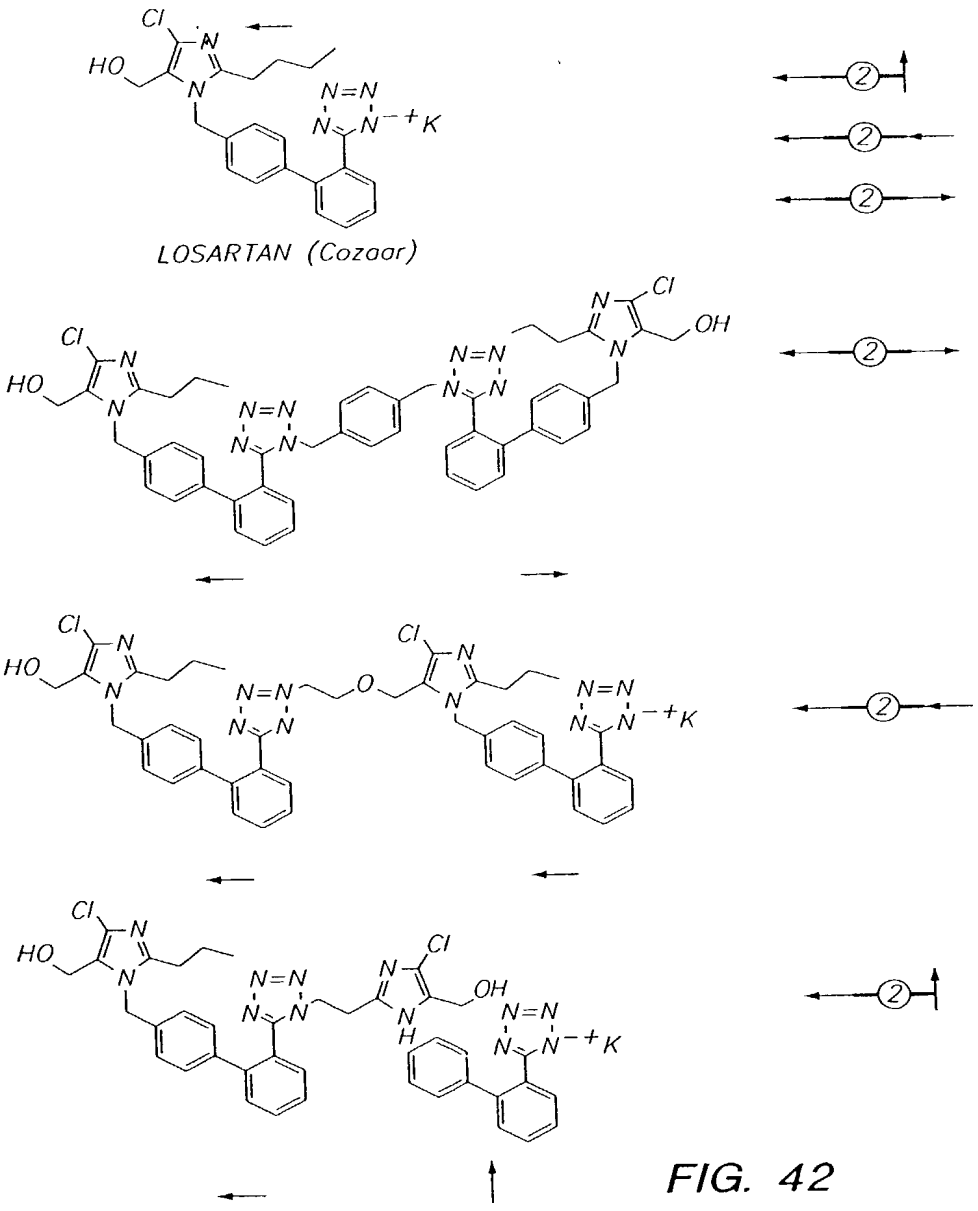
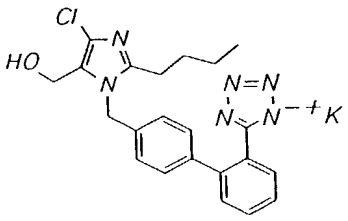
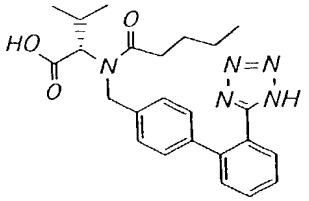


FIG. 42

Losartan Multivalomers 5-Heterovalomers

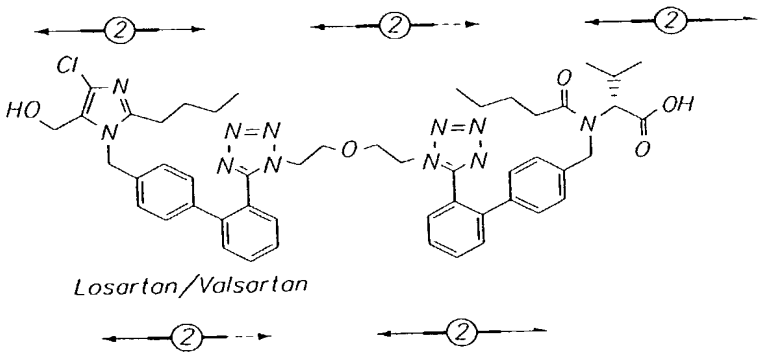


LOSARTAN (Cozaar)



VALSARTAN (Diovan)

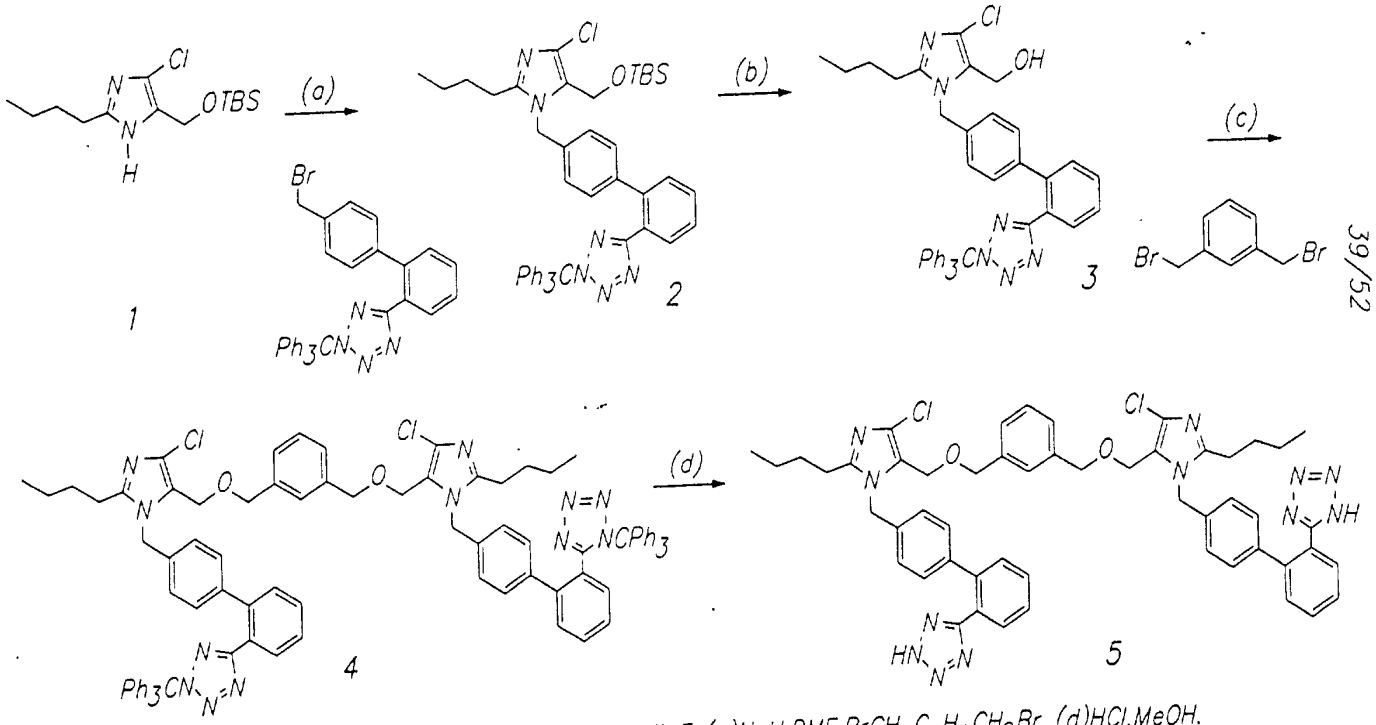
Heterovalomers



Losartan/Valsartan

FIG. 43

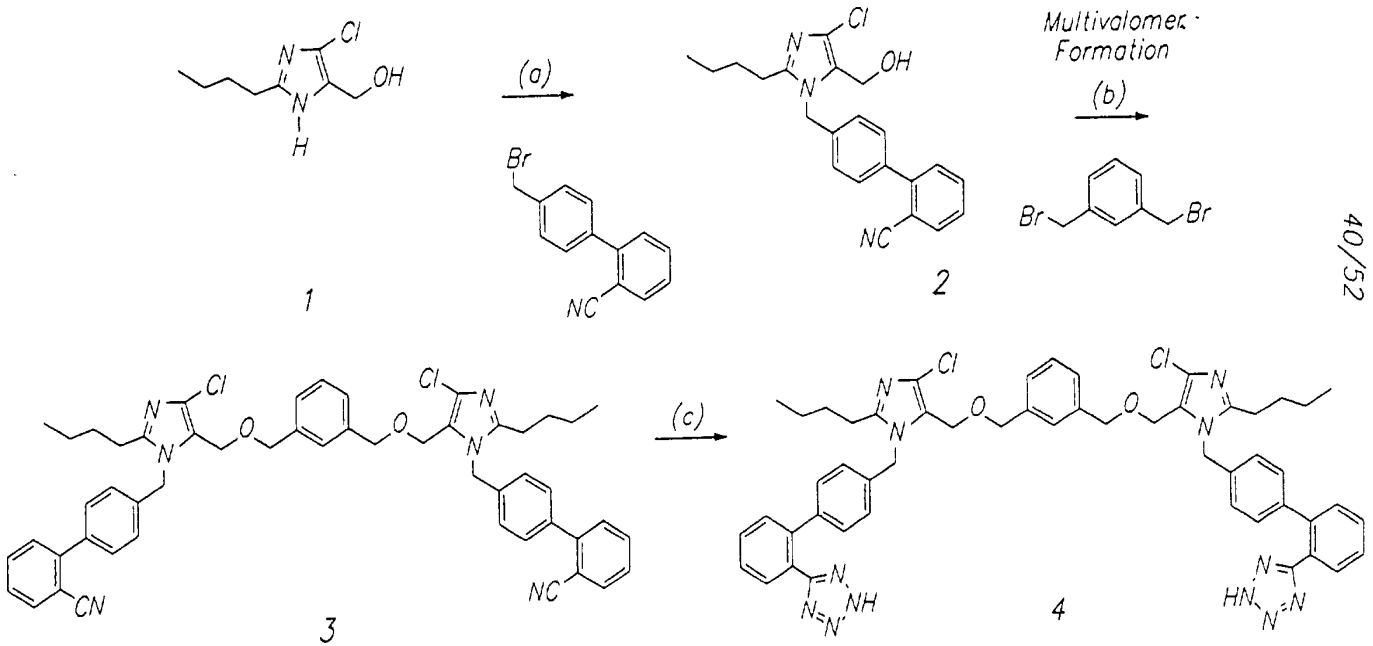
Losartan Multivalomers Synthesis 1-Hydroxyl Linked Multivalomer



(a)NaH, DMF (b)nBu_4NF, THF (c)NaH, DMF, $BrCH_2C_6H_4CH_2Br$ (d)HCl, MeOH.

FIG. 44

Losartan Multivalomer Synthesis 2-Hydroxyl Linked Multivalomer

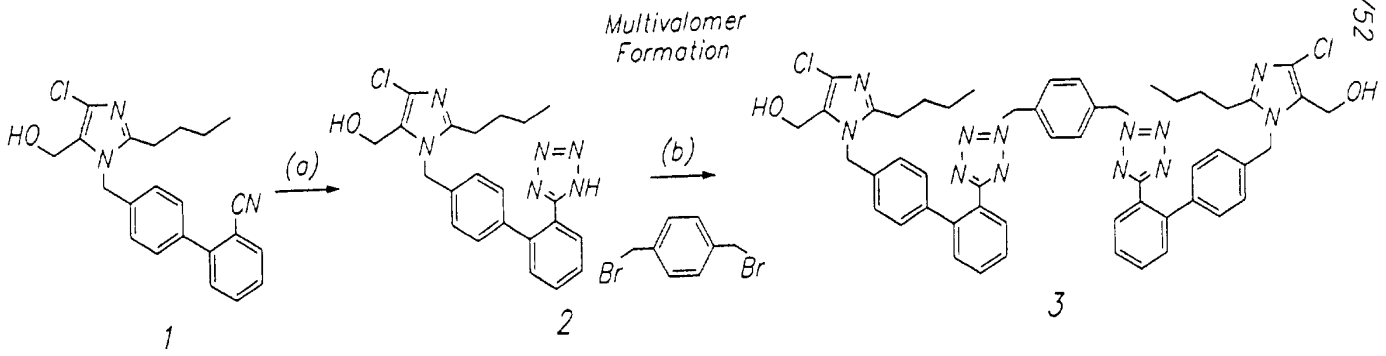


(a)NaOMe,MeOH,DMF (b)NaH,DMF (c)Bu_3SnN_3,xylene,reflux

FIG. 45

Losartan Multivalomer Synthesis 3–Tetrazole Linked Multivalomers

Strategy–Selective tetrazole alkylation in the presence of the primary hydroxyl



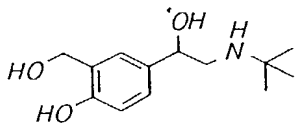
(a)Bu_3SnN_3, xylene, 24hr reflux (b)NaOH, THF

For precedent see Carini, D. J., J. Med. Chem., 1991, 34, 2525–2547

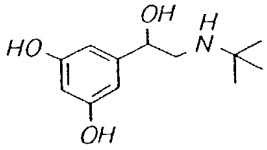
FIG. 46

β_2 Adrenergic Drugs

1. Rapid Onset Inhaled Drugs

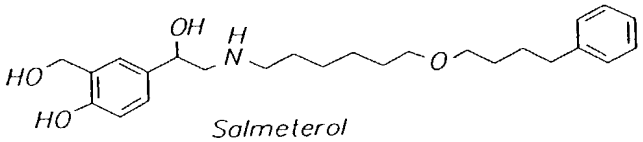


Albuterol
(Glaxo Wellcome)

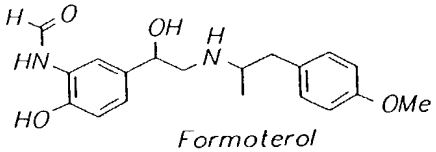


Terbutaline

2. Prolonged Duration of Action Inhaled Drugs



Salmeterol
(Glaxo Wellcome)



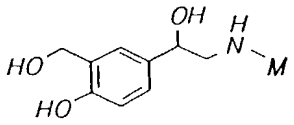
Formoterol
(Novartis)

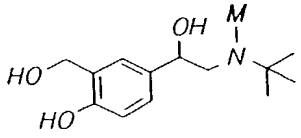
Notes–1 These drugs are racemates.
Multivalomers will produce diastereomers

FIG. 47

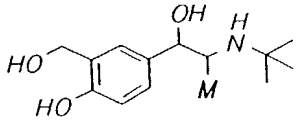
Albuterol Multivalomers

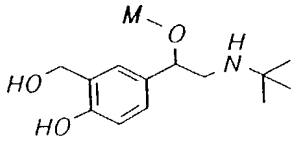
1. N atom





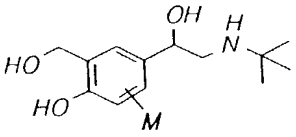
2. Ethanolamine function



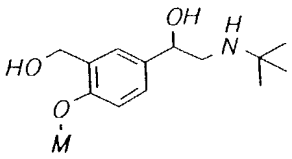


3 Phenyl Ring

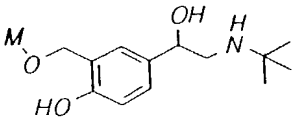
New substitution



Phenolic Group



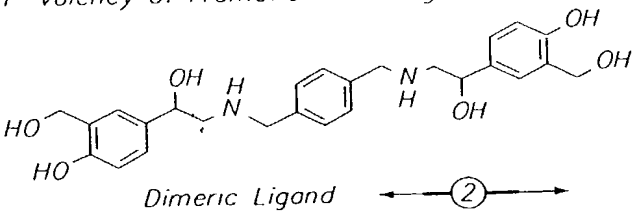
Benzyl Alcohol



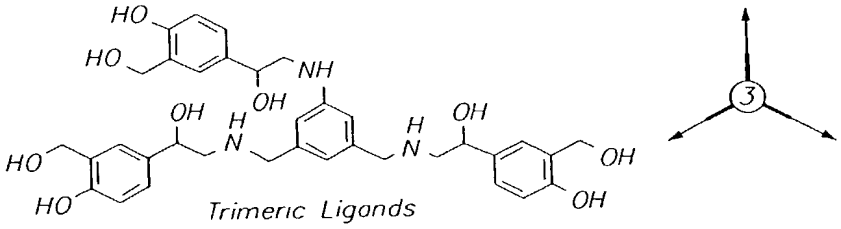
M represents a site for the attachment of the monovalomer to the framework core.

FIG. 48

1 Valency of Framework Building Block

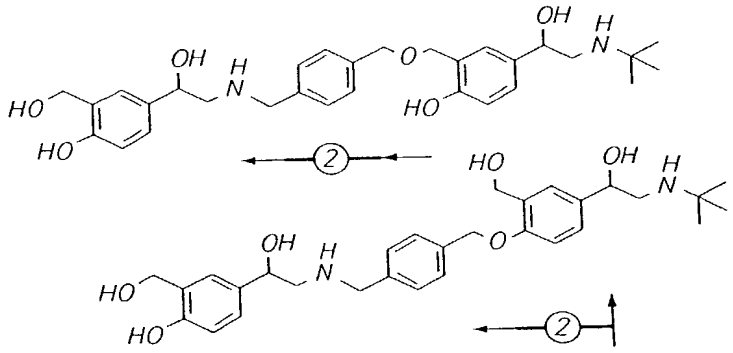


Dimeric Ligand ← (2) →



Trimeric Ligands

2. Relative Orientation of Monovalomer Building Blocks



3 Mixed Multivalomers Derived from Different β_2-agonists

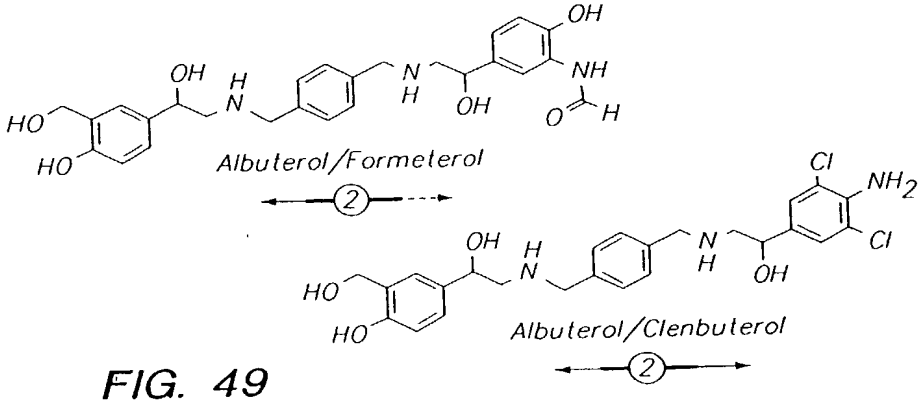


FIG. 49

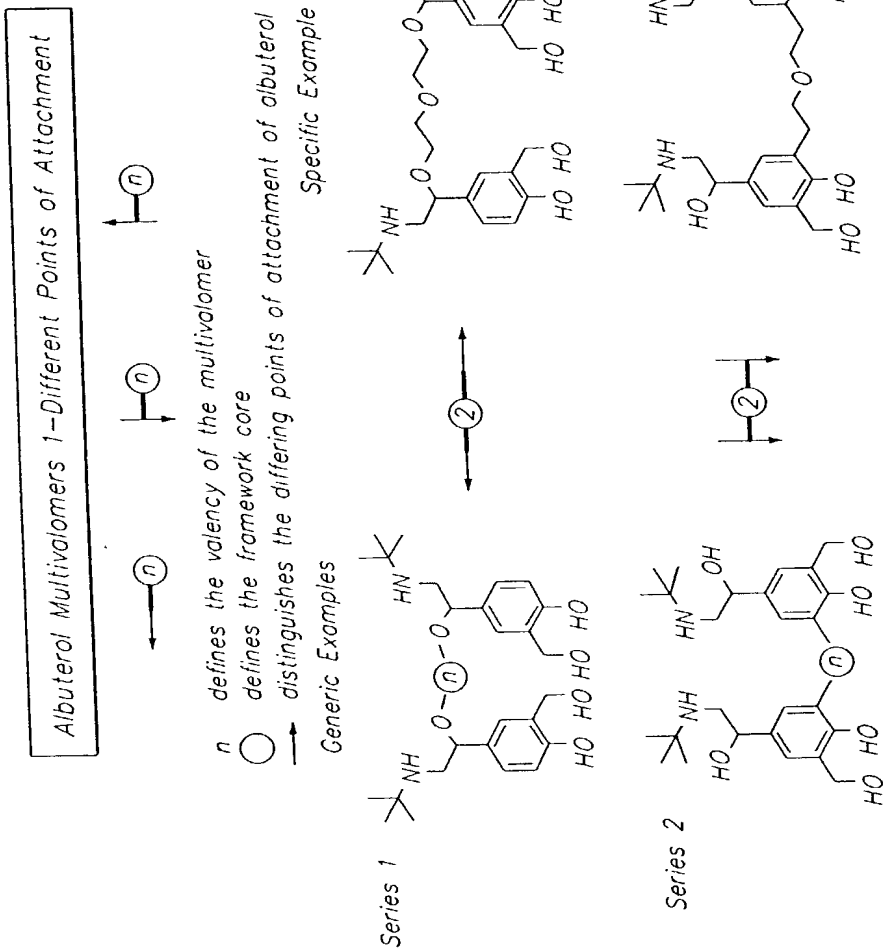

Albuterol Multivalomers 1–Different Points of Attachment
n defines the valency of the multivalomer
defines the framework core
distinguishes the differing points of attachment of albuterol
Generic Exomples
Specific Exomple
Series 1
Series 2

FIG. 50A

FIG. 50B

Albuterol Multivalomers 2--Alternative Framework Cores

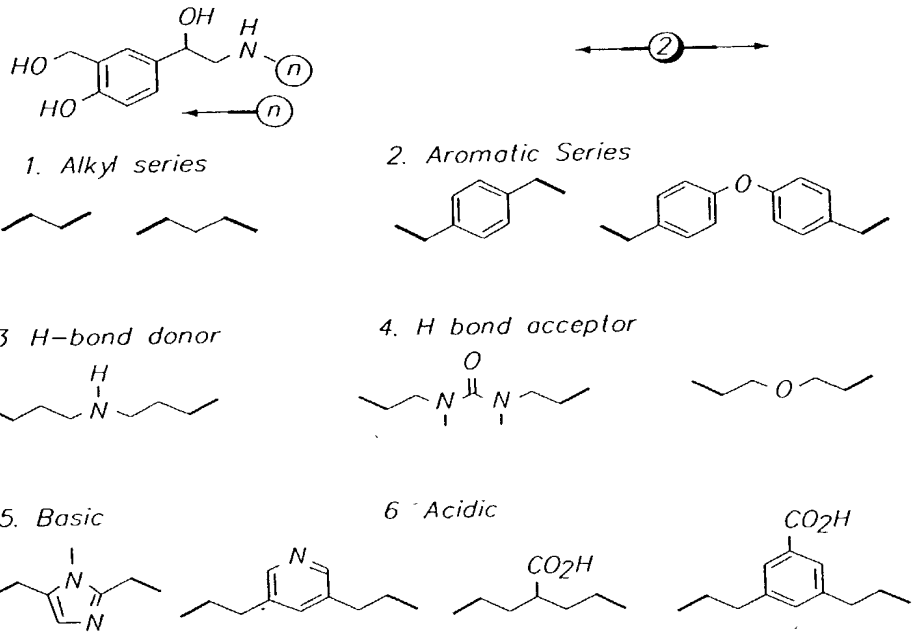


FIG. 51

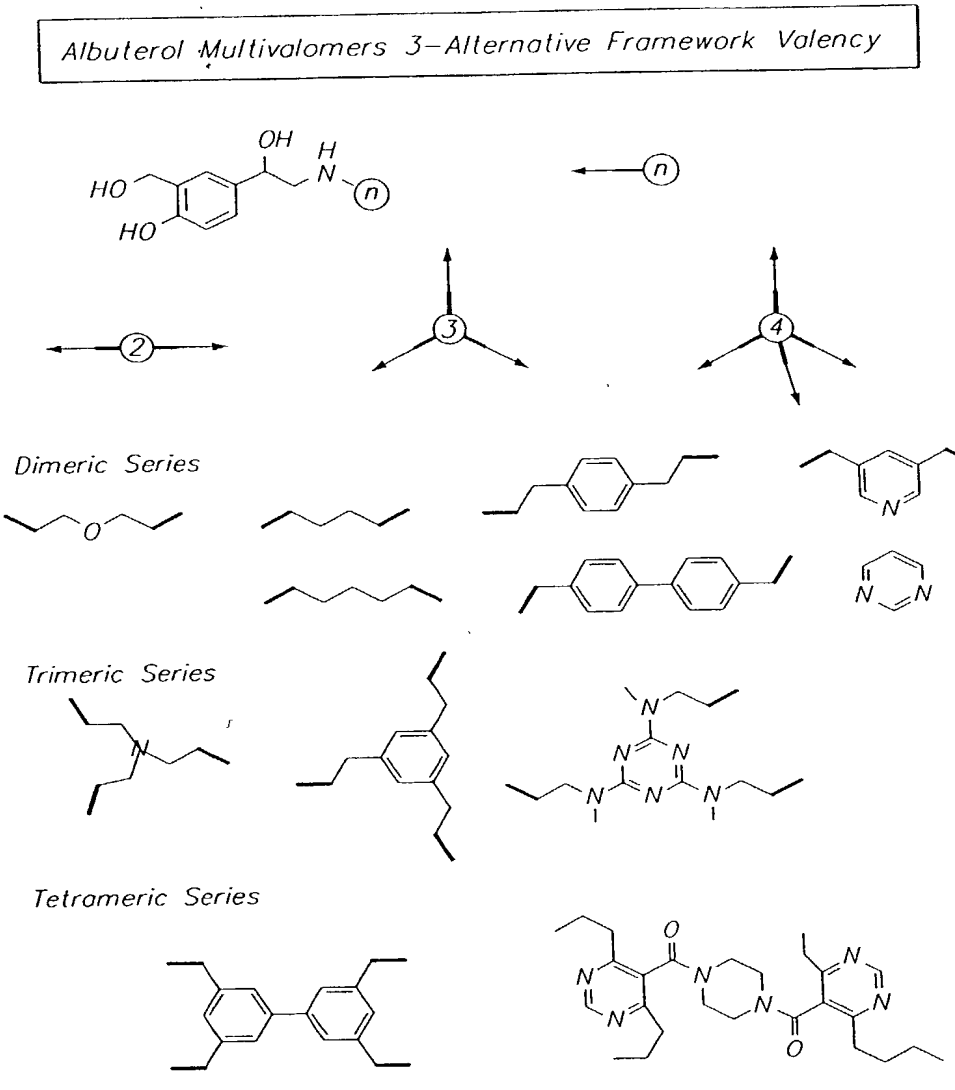

Albuterol Multivalomers 3-Alternative Framework Valency
OH
H
N
n
HO
HO
2
3
4
Dimeric Series
O
N
N
N
Trimeric Series
N
N
N
N
N
N
Tetrameric Series
O
N
N
N
N
N
O

FIG. 52

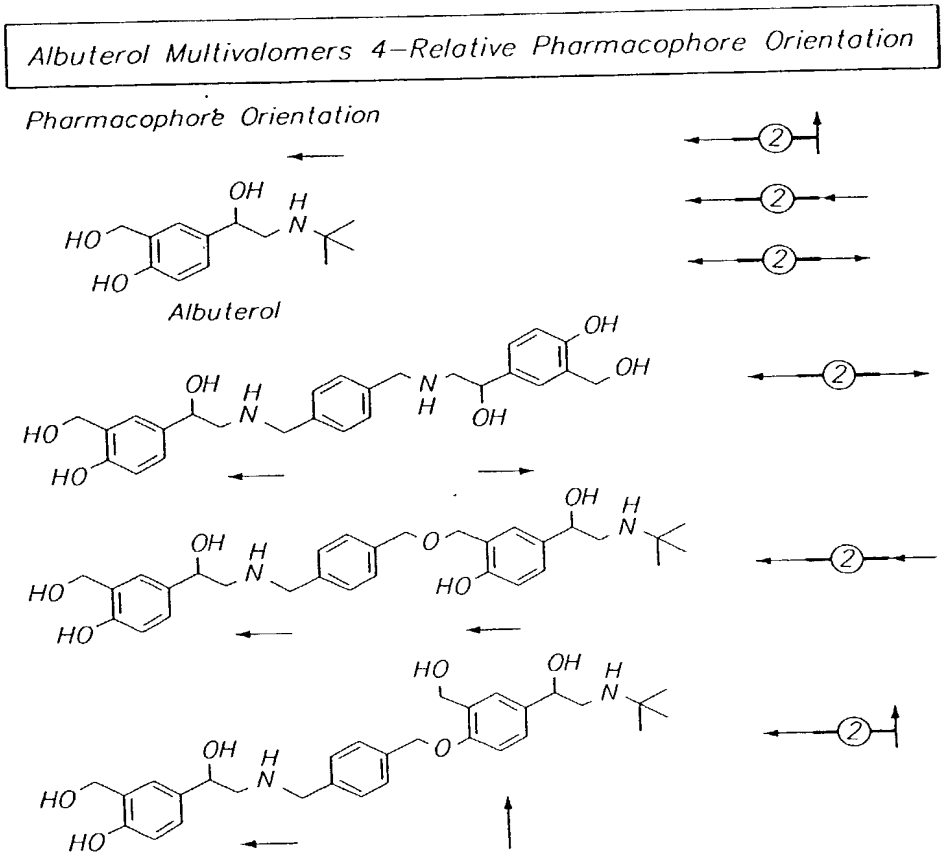

Albuterol Multivalomers 4–Relative Pharmacophore Orientation
Pharmacophore Orientation
Albuterol

FIG. 53

Albuterol Multivalomers 5–Mixed β_2 Adrenergic Heterovalomers

Heterovalomers

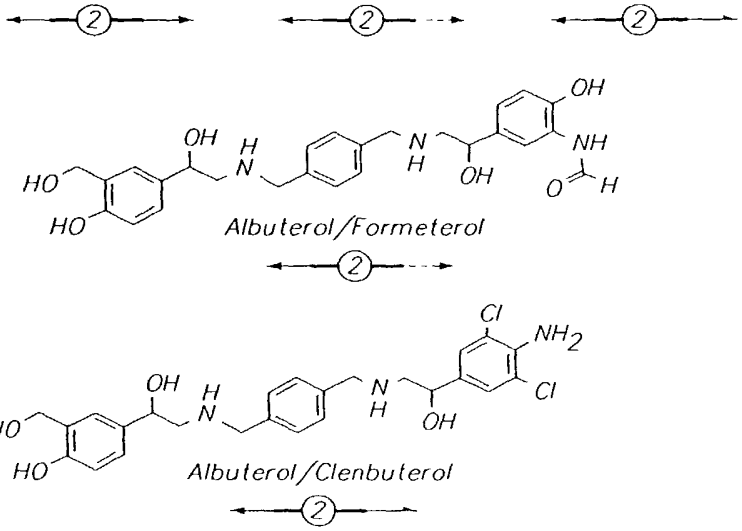
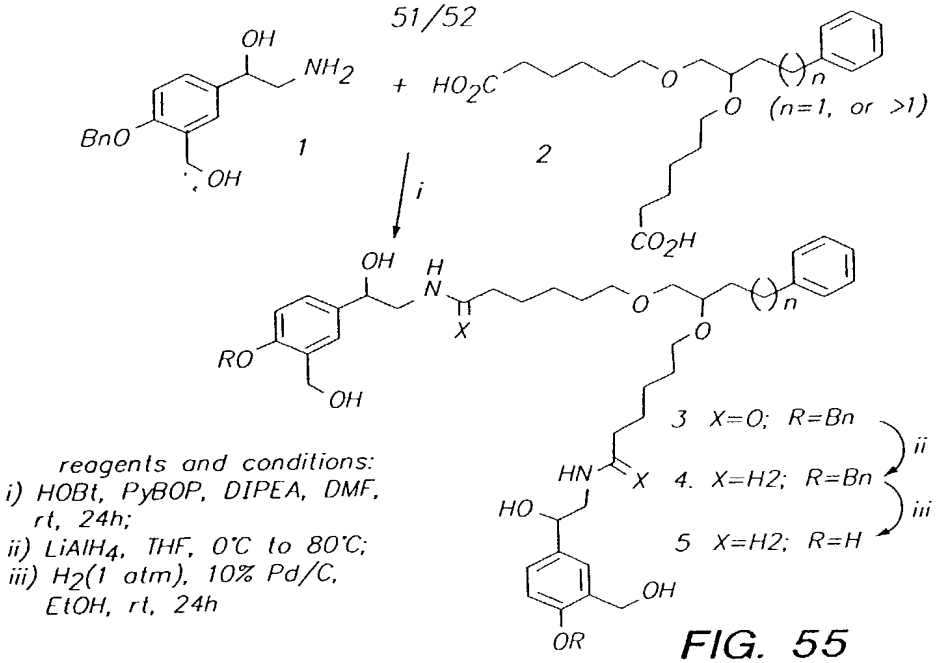
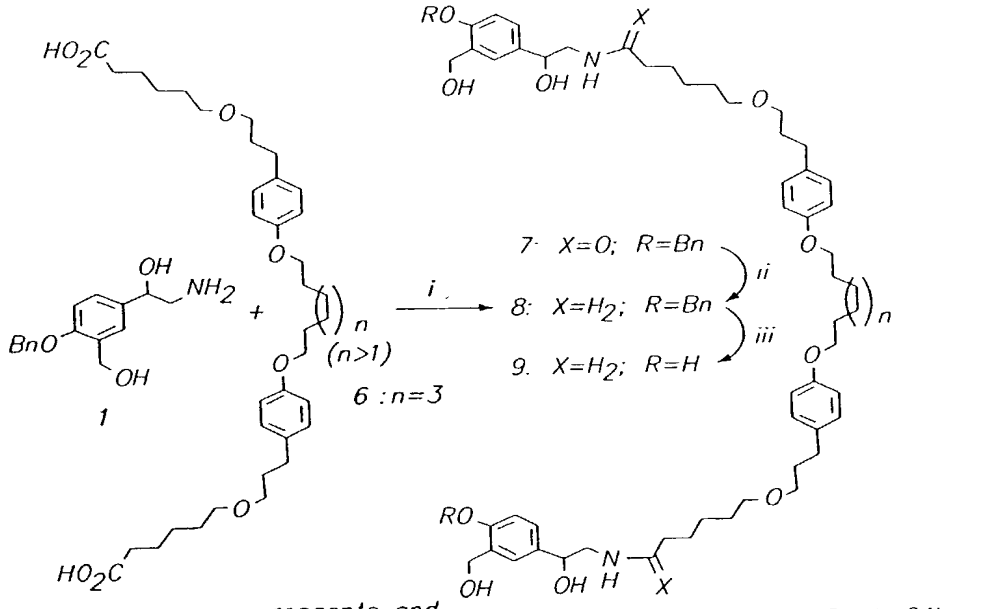


FIG. 54



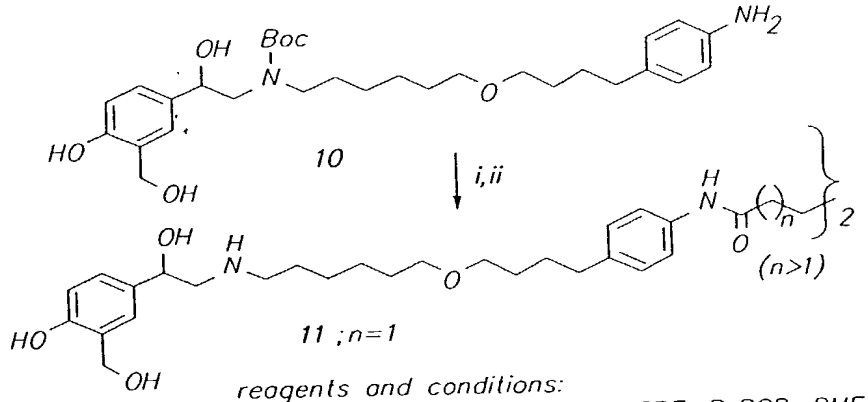
reagents and conditions:
i) HOBt, PyBOP, DIPEA, DMF, rt, 24h;
ii) $LiAlH_4$, THF, 0°C to 80°C;
iii) H_2(1 atm), 10% Pd/C, EtOH, rt, 24h

FIG. 55



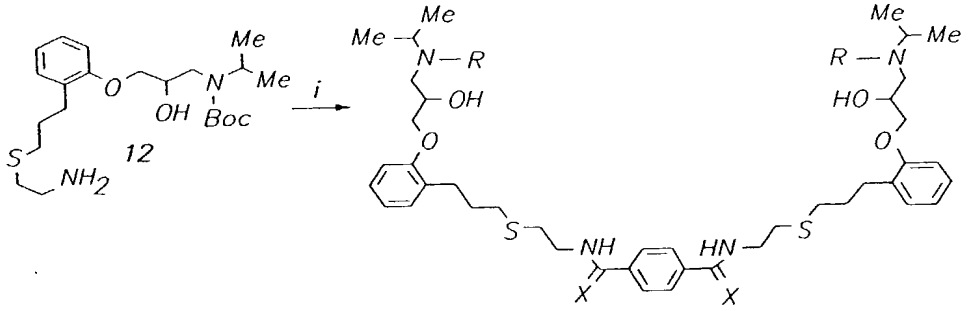
reagents and conditions:
i) HOBt, PyBOP, DIPEA, DMF, rt, 24h;
ii) $LiAlH_4$, THF, 0°C to 80°C;
iii) H_2(1 atm), 10% Pd/C, EtOH, rt, 24h.

FIG. 56



reagents and conditions:
i) 1,6-hexanedioic acid, DIPEA, HOBT, PyBOP, DMF, rt,
ii) TFA/CH_2Cl_2, 0°C.

FIG. 57



ii (13: R=Boc; X=O) iii → 15: R=Boc; X=H2 (ii
14: R=H; X=O 16: R=H; X=H2)

reagents and conditions:
i) terphathalic acid, DIPEA, HOBT, PyBOP, DMF, rt:
ii) TFA/CH_2Cl_2, 0°C:
iii) $LiAlH_4$, THF, 80°C;

FIG. 58